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(21) International Application Number: PCT/US99/10185 (22) International Filing Date: 10 May 1999 (10.05.99) (30) Priority Data: 09/076,592 12 May 1998 (12.05.98) US (71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US). (72) Inventors: WROBEL, Jay, Edward; 15 Rosetree Lane, Lawrenceville, NJ 08648 (US). DIETRICH, Arlene, Joan; 13 Cornell Drive, Delran, NJ 08075 (US). LI, Zenan; 1307 Fox Run Drive, Plainsboro, NJ 08536 (US). (74) Agents: MILOWSKY, Arnold, S.; American Home Products Corporation, Patent Law Dept.- 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: 11-ARYL-BENZO[B]NAPHTHO[2,3-D]FURANS AND 11-ARYL-BENZO[B]NAPHTHO[2,3-D]THIOPHENES USEFUL IN THE TREATMENT OF INSULIN RESISTANCE AND HYPERGLYCEMIA			
<div style="text-align: center;"> <p>(I)</p> </div>			
(57) Abstract The invention provides compounds of formula (I) having a structure wherein A is hydrogen, halogen, or OH; B and D are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, nitro, amino or OR; R is hydrogen, alkyl of 1-6 carbon atoms, -COR ¹ , -CH ₂ CO ₂ R ¹ , -CH(R ^{1a})CO ₂ R ¹ , or -SO ₂ R ¹ ; R ¹ and R ^{1a} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms or aryl; E is S, SO, SO ₂ , O; X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon atoms, nitro, amino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl, or -OCH ₂ CO ₂ R ^{1b} ; R ^{1b} is hydrogen or alkyl of 1-6 carbon atoms; Y and Z are each, independently, hydrogen or OR ² ; R ² is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or -CH ₂ CO ₂ R ³ ; R ³ is hydrogen or alkyl of 1-6 carbon atoms; C is hydrogen, halogen or OR ⁴ ; R ⁴ is hydrogen, alkyl of 1-6 carbon atoms, -CH(R ⁵)W, -C(CH ₃) ₂ CO ₂ R ⁶ , 5-thiazolidine-2,4-dione, -CH(R ⁷)CH ₂ CO ₂ R ⁶ , -COR ⁶ , PO ₃ (R ⁶) ₂ , or -SO ₂ R ⁶ ; R ⁵ is hydrogen, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH ₂ (1H-imidazol-4-yl), -CH ₂ (3-1H-indolyl), -CH ₂ CH ₂ (1,3-dioxo-1,3-dihydro-indol-2-yl), -CH ₂ CH ₂ (1-oxo-1,3-dihydro-indol-2-yl), -CH ₂ (3-pyridyl), or -CH ₂ CO ₂ H; W is -CO ₂ R ⁶ , -CONH ₂ , -CONHOH, CN, -CONH(CH ₂) ₂ CN, 5-tetrazole, -PO ₃ (R ⁶) ₂ , -CH ₂ OH, or -CH ₂ Br, -CONR ⁶ CHR ⁷ CO ₂ R ⁸ , R ⁶ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl; R ⁷ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl; R ⁸ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl; or a pharmaceutically acceptable salt thereof, which are useful in treating metabolic disorders related to insuling resistance or hyperglycemia.			

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**11-ARYL-BENZO[B]NAPHTHO[2,3-D]FURANS AND 11-ARYL-
BENZO[B]NAPHTHO[2,3-D]THIOPHENES USEFUL IN THE TREATMENT
OF INSULIN RESISTANCE AND HYPERGLYCEMIA**

5 BACKGROUND OF THE INVENTION

The prevalence of insulin resistance in glucose intolerant subjects has long been recognized. Reaven et al (*American Journal of Medicine* 1976, 60, 80) used a continuous infusion of glucose and insulin (insulin/glucose clamp technique) and oral glucose tolerance tests to demonstrate that insulin resistance existed in a diverse group of nonobese, nonketotic subjects. These subjects ranged from borderline glucose tolerant to overt, fasting hyperglycemia. The diabetic groups in these studies included both insulin dependent (IDDM) and noninsulin dependent (NIDDM) subjects.

Coincident with sustained insulin resistance is the more easily determined hyperinsulinemia, which can be measured by accurate determination of circulating plasma insulin concentration in the plasma of subjects. Hyperinsulinemia can be present as a result of insulin resistance, such as is in obese and/or diabetic (NIDDM) subjects and/or glucose intolerant subjects, or in IDDM subjects, as a consequence of over injection of insulin compared with normal physiological release of the hormone by the endocrine pancreas.

The association of hyperinsulinemia with obesity and with ischemic diseases of the large blood vessels (e.g. atherosclerosis) has been well established by numerous experimental, clinical and epidemiological studies (summarized by Stout, *Metabolism* 1985, 34, 7, and in more detail by Pyorala et al, *Diabetes/Metabolism Reviews* 1987, 3, 463). Statistically significant plasma insulin elevations at 1 and 2 hours after oral glucose load correlates with an increased risk of coronary heart disease.

Since most of these studies actually excluded diabetic subjects, data relating the risk of atherosclerotic diseases to the diabetic condition are not as numerous, but point in the same direction as for nondiabetic subjects (Pyorala et al). However, the incidence of atherosclerotic diseases in morbidity and mortality statistics in the diabetic population exceeds that of the nondiabetic population (Pyorala et al; Jarrett

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Diabetes/Metabolism Reviews 1989,5, 547; Harris et al, Mortality from diabetes, in *Diabetes in America* 1985).

The independent risk factors obesity and hypertension for atherosclerotic diseases are also associated with insulin resistance. Using a combination of insulin/glucose clamps, tracer glucose infusion and indirect calorimetry, it has been demonstrated that the insulin resistance of essential hypertension is located in peripheral tissues (principally muscle) and correlates directly with the severity of hypertension (DeFronzo and Ferrannini, *Diabetes Care* 1991, 14, 173). In hypertension of the obese, insulin resistance generates hyperinsulinemia, which is recruited as a mechanism to limit further weight gain via thermogenesis, but insulin also increases renal sodium reabsorption and stimulates the sympathetic nervous system in kidneys, heart, and vasculature, creating hypertension.

It is now appreciated that insulin resistance is usually the result of a defect in the insulin receptor signaling system, at a site post binding of insulin to the receptor. Accumulated scientific evidence demonstrating insulin resistance in the major tissues which respond to insulin (muscle, liver, adipose), strongly suggests that a defect in insulin signal transduction resides at an early step in this cascade, specifically at the insulin receptor kinase activity, which appears to be diminished (reviewed by Haring, *Diabetologia* 1991, 34, 848).

Protein-tyrosine phosphatases (PTPases) play an important role in the regulation of phosphorylation of proteins. The interaction of insulin with its receptor leads to phosphorylation of certain tyrosine molecules within the receptor protein, thus activating the receptor kinase. PTPases dephosphorylate the activated insulin receptor, attenuating the tyrosine kinase activity. PTPases can also modulate post-receptor signaling by catalyzing the dephosphorylation of cellular substrates of the insulin receptor kinase. The enzymes that appear most likely to closely associate with the insulin receptor and therefore, most likely to regulate the insulin receptor kinase activity, include PTP1B, LAR, PTP α and SH-PTP2 (B. J. Goldstein, *J. Cellular Biochemistry* 1992, 48, 33; B. J. Goldstein, *Receptor* 1993, 3, 1-15; F. Ahmad and B. J. Goldstein *Biochim. Biophys Acta* 1995, 1248, 57-69).

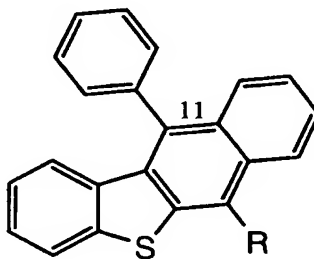
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McGuire et al. (*Diabetes* 1991, 40, 939), demonstrated that nondiabetic glucose intolerant subjects possessed significantly elevated levels of PTPase activity in muscle tissue vs. normal subjects, and that insulin infusion failed to suppress PTPase activity as it did in insulin sensitive subjects.

5 Meyerovitch et al (*J. Clinical Invest.* 1989, 84, 976) observed significantly increased PTPase activity in the livers of two rodent models of IDDM, the genetically diabetic BB rat, and the STZ-induced diabetic rat. Sredy et al (*Metabolism*, 44, 1074, 1995) observed similar increased PTPase activity in the livers of obese, diabetic ob/ob mice, a genetic rodent model of NIDDM.

10 The compounds of this invention have been shown to inhibit PTPases derived from rat liver microsomes and human-derived recombinant PTPase-1B (hPTP-1B) *in vitro*. They are useful in the treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels.

15 K. Shinzo, et al., *Heterocycles* **1982**, 19, 1033-1037 disclosed a synthesis of benzo[b]naphtho[2,3-d]thiophenes of which two examples also had a 11-phenyl substituent as shown by structure A below. None of the examples in this *Heterocycles* article contained the appropriate substitution, nor any substitution on the 11-phenyl group necessary for *in vitro* PTPase inhibition activity or *in vivo* antidiabetic activity.



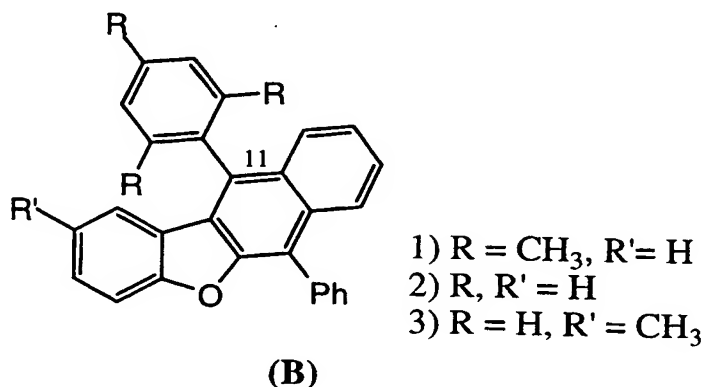
(A), R = H, CH₃

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J. Hastings, et al., *J. Chem. Soc., Perkin Trans. 1* **1975**, 19, 1995-1998 and J. Hastings, et al., *J. Chem. Soc., Perkin Trans. 1* **1972**, 14, 1839-1842 disclosed three examples of benzo[b]naphtho[2,3-d]furans that also had a 11-phenyl substituent as shown by structure B below. None of the examples in these *J. Chem. Soc., Perkin*

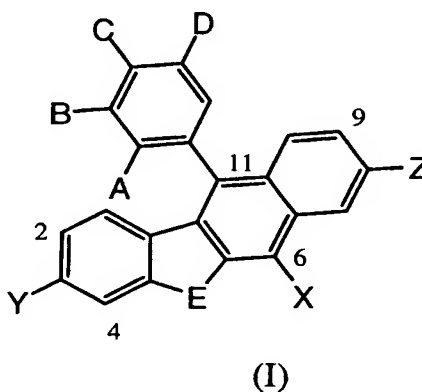
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Trans. 1 articles contained the appropriate substitution on the 11-phenyl group necessary for in vitro PTPase inhibition activity or in vivo antidiabetic activity.



5 DESCRIPTION OF THE INVENTION

This invention provides a compound of formula I having the structure



wherein

- 10 A is hydrogen, halogen, or OH;
 B and D are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, nitro, amino or OR;
 R is hydrogen, alkyl of 1-6 carbon atoms, -COR¹, -CH₂CO₂R¹, -CH(R^{1a})CO₂R¹, or -SO₂R¹;
 15 R¹ and R^{1a} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms or aryl;

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E is S, SO, SO₂, O;

X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon atoms, nitro, amino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl, or -OCH₂CO₂R^{1b};

R^{1b} is hydrogen or alkyl of 1-6 carbon atoms;

Y and Z are each, independently, hydrogen or OR²;

R² is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or -CH₂CO₂R³;

10 R³ is hydrogen or alkyl of 1-6 carbon atoms;

C is hydrogen, halogen or OR⁴;

R⁴ is hydrogen, alkyl of 1-6 carbon atoms, -CH(R⁵)W, -C(CH₃)₂CO₂R⁶, 5-thiazolidine-2,4-dione, -CH(R⁷)CH₂CO₂R⁶, -COR⁶, PO₃(R⁶)₂, or -SO₂R⁶;

R⁵ is hydrogen, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH₂(1H-imidazol-4-yl),

15 -CH₂(3-1H-indolyl), -CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl),

-CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), -CH₂(3-pyridyl), or

-CH₂CO₂H;

W is -CO₂R⁶, -CONH₂, -CONHOH, CN, -CONH(CH₂)₂CN, 5-tetrazole, -PO₃(R⁶)₂, -CH₂OH, or -CH₂Br, -CONR⁶CHR⁷CO₂R⁸,

20 R⁶ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

R⁷ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

R⁸ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

or a pharmaceutically acceptable salt thereof, which are useful in treating metabolic disorders related to insulin resistance or hyperglycemia.

25

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric,

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sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic moiety, such as when R⁵ is -CH₂(3-pyridyl) or contains similar basic moieties. Salts may also be formed from organic and inorganic bases, preferably alkali metal salts, for example, sodium, lithium, or potassium, when a compound of this invention contains a carboxylate or phenolic moiety.

Alkyl includes both straight chain as well as branched moieties. Halogen means bromine, chlorine, fluorine, and iodine. It is preferred that the aryl portion of the aryl or aralkyl substituent is a phenyl or naphthyl; with phenyl being most preferred. The aryl moiety may be optionally mono-, di-, or tri- substituted with a substituent selected from the group consisting of alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, trifluoromethyl, halogen, alkoxycarbonyl of 2-7 carbon atoms, alkylamino of 1-6 carbon atoms, and dialkylamino in which each of the alkyl groups is of 1-6 carbon atoms, nitro, cyano, -CO₂H, alkylcarbonyloxy of 2-7 carbon atoms, and alkylcarbonyl of 2-7 carbon atoms.

The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry in Formula I, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

The compounds of this invention may be atropisomers by virtue of possible restricted or slow rotation about the aryl-tetracyclic single bond. This restricted rotation creates additional chirality and leads to enantiomeric forms. If there is an additional chiral center in the molecule, diastereomers exist and can be seen in the NMR and via other analytical techniques. While shown without respect to

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atropisomer stereochemistry in Formula I, the present invention includes such atropisomers (enantiomers and diastereomers; as well as the racemic, resolved, pure diastereomers and mixtures of diastereomers) and pharmaceutically acceptable salts thereof.

5

Preferred compounds of this invention include compounds of formula (I) in which

A and B are each, independently, hydrogen, or bromine;

C and D are OH;

10 E is S, or O;

X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, alkoxy of 1-6 carbon atoms, aryloxy of 6-12 carbon atoms; arylalkoxy of 6-12 carbon atoms, arylsulfanyl, or pyridylsulfanyl;

Y and Z are H;

15 or a pharmaceutically acceptable salt thereof.

Other preferred compounds of this invention include compounds of formula (I) in which

A is hydrogen;

20 B and D are each, independently, halogen, alkyl of 1-6 carbon atoms, aryl or aralkyl of 6-12 carbon atoms, or alkoxy of 1-6 carbon atoms;

C is OR⁴

E is S, O;

25 X is hydrogen, halogen, alkyl of 1-6 carbon atoms, perfluoroalkyl of 1-6 carbon atoms, CN, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon atoms, arylsulfanyl, pyridylsulfanyl;

Y and Z are H;

R⁴ is H, alkyl of 1-6 carbon atoms, -CH(R⁵)W, or 5-thiazolidine-2,4-dione;

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R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, aryl, -CH₂(3-1H-indolyl), -CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl), -CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), or -CH₂(3-pyridyl);

W is -CO₂R⁶, -CONH₂, -CONHOH, -5-tetrazole, or -PO₃(R⁶)₂;

- 5 R⁶ is hydrogen or alkyl of 1-6 carbon atoms;
or a pharmaceutically acceptable salt thereof.

More preferred compounds of this invention include:

- 10 (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-phenoxy]-3-phenyl-propionic acid;
- (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- 15 (5'-benzo[b]naphtho[2,3-d]thiophen-11-yl)-[1,1';3',1'']terphenyl-2'-yloxy)-acetic acid;
- 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenoxy)-acetic acid;
- 20 acid;
- (R)-2-[2,6-dibromo-4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- 25 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(4-fluorophenyl-propionic acid;
- (R)-2-[2-bromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-6-methoxy-phenoxy]-3-phenyl-propionic acid;
- 30 (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid;

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(R)-2-[2,6-dibromo-4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid;

- 5 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-hexanoic acid;

(R)-2-[2,6-dibromo-4-(6-methoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;

- 10 (R)-2-[2,6-dibromo-4-(6-chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;

- 15 (R)-2-[2,6-dibromo-4-(6-phenylsulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid;

(R)-2-[2,6-dibromo-4-(6-phenylsulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;

- 20 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(1H-indol-3-yl)-propionic acid;

(R)-2-[2,6-diiodo-4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;

- 25 (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-butyric acid;

- 30 (R)-2-[2,6-dibromo-4-(6-trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;

(S)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-butyric acid;

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- (R)-2-(4-benzo[b]naphtho[2,3-d]thiophen-11-yl-2,6-dibromo-phenoxy)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid;
- (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-
5 (1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid;
- {1-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propyl}-phosphonic acid;
- 10 (R)-2-[2,6-dibromo-4-(6-(pyridin-4-ylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- (R)-2-[2,6-dibromo-4-(6-benzyloxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- 15 (S)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-2-
20 phenyl-acetic acid;
- [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid;
- 25 [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy-methyl]-phosphonic acid;
- (S)-2-[2,6-dibromo-4-(6-cyano-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- 30 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(naphthalen-2-yl)-propionic acid;

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- (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1-oxo-1,3-dihydro-isoindol-2-yl)-butyric acid;
- (R)-2-[2,6-dibromo-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- (R)-5-{1-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-2-phenyl-ethyl}-1H-tetrazole;
- (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-N-hydroxy-3-phenyl-propionamide;
- 5-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-thiazolidine-2,4-dione;
- (R)-2-[2,6-diiodo-4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]--propionic acid;
- 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-pyridin-3-yl-propionic acid;
- (R)-2-[4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenoxy]-3-phenyl-propionic acid;
- (R)-2-[4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenoxy]-propionic acid;
- 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol;
- 3-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol;
- 4-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol;
- [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-phenoxy]-acetic acid;

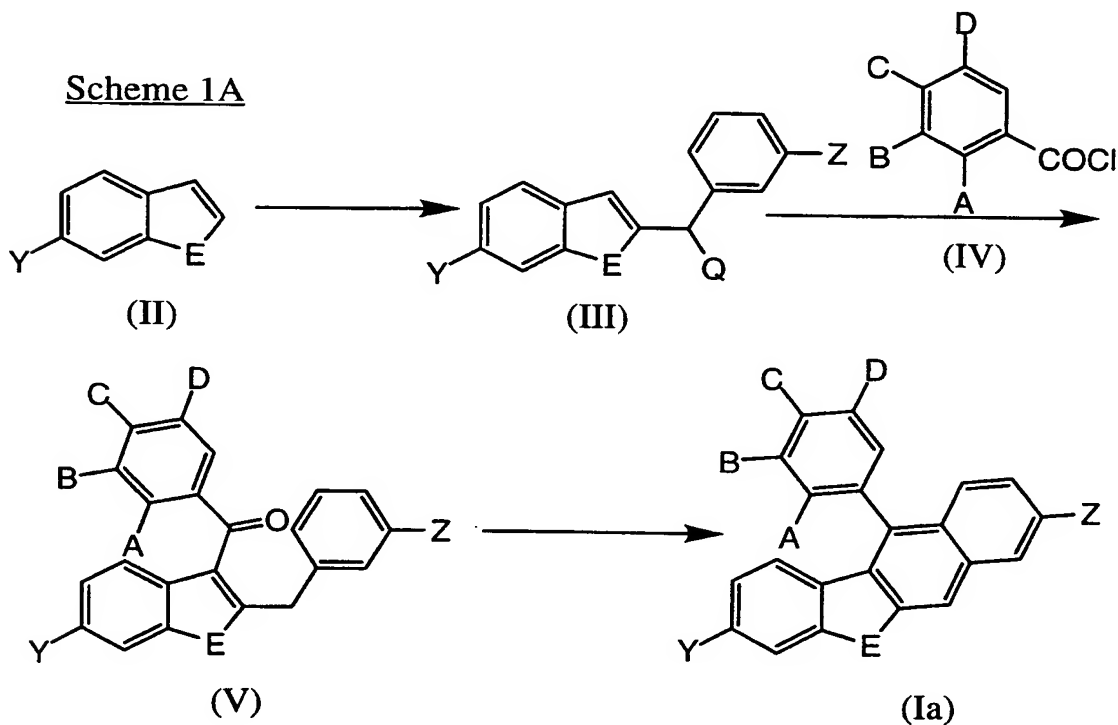
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2, 6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11yl)-phenol;

or pharmaceutically acceptable salts thereof.

5

The compounds of this invention can be prepared according to the following schemes from commercially available starting materials or starting materials which can be prepared using to literature procedures. These schemes show the preparation of representative compounds of this invention.



10

In Scheme 1A, commercially available thianaphthene (II: Y = H; E is S) or benzofuran (II: Y = H; E is O) is treated with one to 1.3 molar equivalents of an alkyl lithium reagent such as N-butyl lithium most preferably in a nonprotic solvent such as THF at temperatures ranging from -78°C to room temperature under an inert atmosphere such as nitrogen or argon to provide the 2-lithiated-thianaphthene or benzofuran derivative. This lithiated analog is reacted in situ with one or more molar equivalents of benzaldehyde, generally at -78°C to room temperature for 5 min to 3 h

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to provide the compound of formula (III: Y, Z = H; Q = OH; E is S or O). The hydroxy group (Q = OH) of (III) can be removed by a number of reduction procedures such as hydrogenation using palladium catalysts to produce the compound of formula (III: Q, Y, Z = H; E is S or O) but is most conveniently removed using the method of Nutaitis, et. al. (*Org. Prep. and Proceed. Int.* **1991**, 23, 403-411) in which (III: Y, Z = H; Q = OH; E is S or O) is stirred with one to ten molar equivalents of sodium borohydride in a suitable solvent such as ether, THF or dichloromethane at 0°C to room temperature and one to fifty molar equivalents of trifluoroacetic acid is slowly added over a 15 min to 3 h period to produce the compound of formula (III: Q, Y, Z = H; E is S or O). Alternatively, the 2-lithiated analog of thianaphthene (II: Y = H; E is S) or benzofuran (II: Y = H; E is O), in a nonprotic solvent such as THF, can be reacted with one or more molar equivalents of a benzyl halide such as benzyl bromide (PhCH₂Br) at -78°C to room temperature to directly provide the compound of formula (III: Q, Y, Z = H; E is S or O).

In an analogous fashion, 6-methoxythianaphthene (II: Y = OMe; E is S, S. L. Graham, et al., *J. Med. Chem.* **1989**, 32, 2548-2554) can be used as starting material using the above sequences to provide the compound of formula (III: Q, Z = H; Y = OMe; E is S). Still, alternatively, using the above sequences and starting from thianaphthene (II: Y = H; E is S) or benzofuran (II: Y = H; E is O), 3-methoxybenzaldehyde (o-anisaldehyde) can be used in place of benzaldehyde to prepare the compound of formula (III: Q, Y = H; Z = OMe; E is S or O). The latter compound (III: Q, Y = H, Z = OMe; E is S or O) can also be prepared from a 3-methoxybenzyl halide such as 3-methoxybenzyl bromide and the 2-lithiated analog of thianaphthene (II: Y = H; E is S) or benzofuran (II: Y = H; E is O) as described above.

The compounds of formula (III: Q = H; Y, Z is H or OMe; E is S or O) can be acylated with one or more molar equivalents of a commercially available benzoic acid chloride of formula (IV: A, B, C, D is H or OMe; with the A, B, C, D, combination of substituents having at least one OMe group but not more than three OMe groups) to produce the acylated derivative of formula (V: A, B, C, D is H or OMe; with the A, B,

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C, D, combination of substituents having at least one OMe group but not more than three OMe groups; Y, Z is H or OMe; E is S or O). This acylation is accomplished most readily using a one to five molar equivalents of a Lewis acid catalyst such as tin tetrachloride or aluminum chloride in an inert solvent such as dichloromethane, 1, 2-dichloroethane or carbon disulfide, generally at temperatures such as -78°C to room temperature.

Cyclization of the compounds of formula (V: A, B, C, D is H or OMe; with the A, B, C, D, combination of substituents having at least one OMe group but not more than three OMe groups; Y, Z is H or OMe; E is S or O) is generally best accomplished using one to ten molar equivalents of a strong Lewis acid such as a trihaloborane, most conveniently tribromoborane. The reaction is best performed at -78°C with warming to room temperature in a halocarbon solvent such as dichloromethane under an inert atmosphere such as nitrogen or argon. These procedures not only effect cyclization and aromatization with concomitant loss of water, but also result in demethylation of any pendant methoxy moieties and result in the production of compounds of formula (Ia: A, B, C, D is H or OH; with the A, B, C, D, combination of substituents having at least one OH group but not more than three OH groups; Y, Z is H or OH; E is S or O).

In the cases in which the compound of formula (III: Q, Y = H; Z = OMe; E is S or O) contains a methoxy moiety in position Z, acylation with the compound of formula (IV: A, B, D is H; C is OMe; E is S or O) is effected as usual with a Lewis acid catalyst such as tin tetrachloride to produce the compound of formula (V: A, B, D, Y is H; C, Z is OMe; E is S or O) in situ. This compound, by virtue of its Z = OMe moiety, is activated to further facile cyclization under the acylation conditions to provide directly the compound of formula (Ia: A, B, D, Y is H; C, Z is OMe; E is S or O). This compound can then be demethylated using boron tribromide or boron trichloride to produce the compound of formula (Ia: A, B, D, Y is H; C, Z is OH; E is S or O).

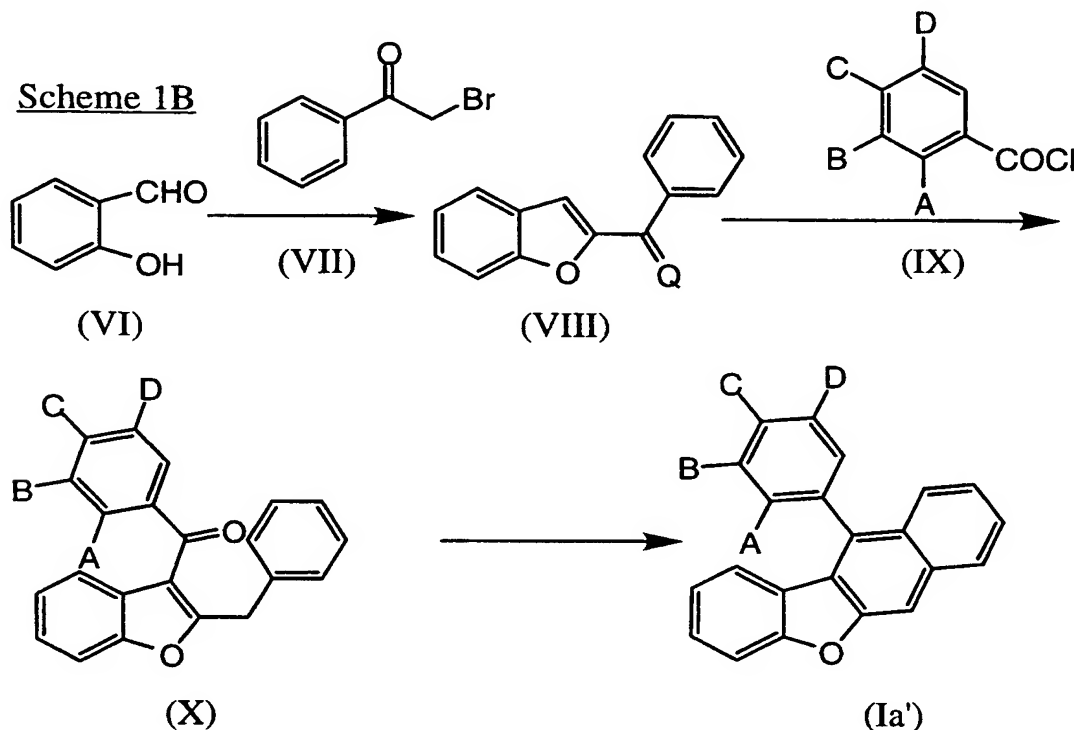
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In an analogous fashion to the reactions above in Scheme 1A, the compounds of formula (Ia: A is H; B, D is alkyl of 1-6 carbon atoms; C is OH; Y, Z is H; E is S or O) can be prepared starting from the compound of formula (III: Q, Y, Z is H; E is S or O) and the appropriate benzoic acid chloride (IV: A is H; B, D is alkyl of 1-6 carbon atoms; C is OMe). The benzoic acid chloride (IV: A is H; B, D is alkyl of 1-6 carbon atoms; C is OMe) is prepared from the corresponding benzoic acid by standard procedures using reagents such as oxalyl chloride and thionyl chloride. The starting benzoic acid of the benzoic acid chloride (IV: A is H; B, D is alkyl of 1-6 carbon atoms; C is OMe) is commercially available or can be easily prepared by known procedures. For example, the acid starting material for benzoic acid chloride (IV: A is H; B, D is isopropyl; C is OMe) can be prepared using a modification of the method of Schuster, et al., *J. Org. Chem* **1988**, *53*, 5819. Thus commercially available 2, 6-diisopropyl phenol is brominated in the 4-position (bromine / acetic acid), methylated (iodomethane / potassium carbonate / DMF), reacted with n-butyl lithium to effect lithium halogen exchange and the resultant organolithium species is reacted with carbon dioxide to provide 3, 5-diisopropyl, 4-methoxy benzoic acid.

The compounds of formula (Ia: A, C is F; D is H; B is OH; Y, Z is H; E is S or O) can be prepared starting from the compound of formula (III: Q, Y, Z is H; E is S or O) and the appropriate benzoic acid chloride (IV: A, C is F; D is H; B is OMe). The benzoic acid chloride (IV: A, C is F; D is H; B is OMe) is prepared from the corresponding benzoic acid by standard procedures using reagents such as oxalyl chloride and thionyl chloride. The starting benzoic acid of the benzoic acid chloride (IV: A, C is F; D is H; B is OMe) can be easily prepared from the known, 4-bromo-2, 6-difluoroaniline (L. I. Kruse, et al., *Biochemistry* **1986**, *25*, 7271-7278) by reacting the latter compound with n-butyl lithium to effect deprotonation ortho to the bromine and fluorine atoms, reaction of the resultant organolithium species with carbon dioxide to install the carboxy moiety ortho to the bromine and fluorine atoms, and further reaction with n-bultyl lithium to effect lithium-bromine exchange and reaction of the final, resultant organolithium species with a proton source upon aqueous workup to provide 2, 4-difluoro, 3-methoxy benzoic acid. Precedence for the fluorine

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directed ortholithiation reaction over lithium-bromine exchange reaction is found in the following paper: F. Mongin and M. Schlosser, *Tetrahedron Lett.* **1996**, 37, 6551-6554.



- 5 In Scheme 1B, according to a procedure in *Syn. Comm.* **1987**, 17, 341-354 commercially available salicylaldehyde (VI) is reacted with one molar equivalent of, 2-bromacetophenone (VII), one or more molar equivalents of potassium carbonate and 5 mole % of tetrabutylammonium sulfate in a biphasic mixture of water and dichloromethane at room temperature to provide the compound of formula (VIII: Q =
- 10 O). The ketone group (Q = O) of (VIII) can be reduced under Wolf-Kishner conditions (hydrazine, followed by potassium hydroxide in diethylene glycol reflux) to produce the compound of formula (VIII: Q = H₂).

- The compounds of formula (VIII: Q = H₂) can be acylated with one or more molar equivalents of a commercially available benzoic acid chloride of formula (IX:
- 15 A, B, C, D is H or OMe; with the A, B, C, D, combination of substituents having at least one OMe group but not more than three OMe groups) to produce the acylated derivative of formula (X: A, B, C, D is H or OMe; with the A, B, C, D, combination

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of substituents having at least one OMe group but not more than three OMe groups). This acylation is accomplished most readily using a one to five molar equivalents of a Lewis acid catalyst such as tin tetrachloride or aluminum chloride in an inert solvent such as dichloromethane, 1, 2-dichloroethane or carbon disulfide, generally at
5 temperatures such as -78°C to room temperature.

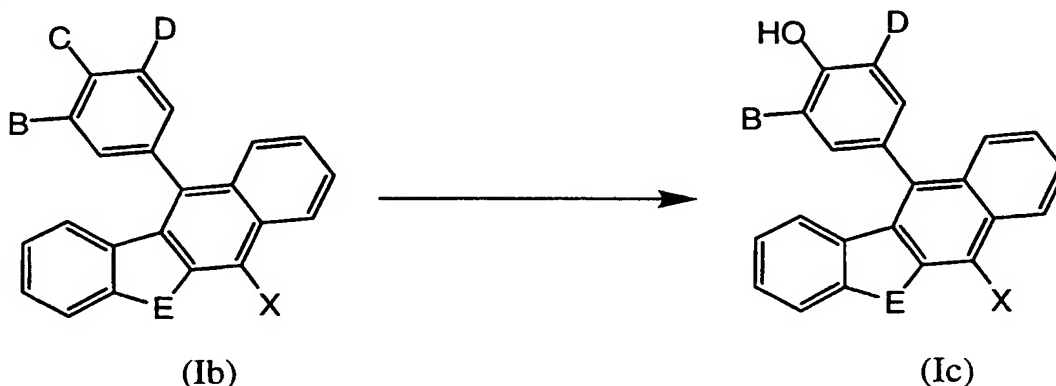
Cyclization of the compounds of formula (X: A, B, C, D is H or OMe; with the A, B, C, D, combination of substituents having at least one OMe group but not more than three OMe groups) is generally best accomplished using one to ten molar equivalents of a strong Lewis acid such as a trihaloborane, most conveniently
10 tribromoborane. The reaction is best performed at -78°C with warming to room temperature in a halocarbon solvent such as dichloromethane under an inert atmosphere such as nitrogen or argon. These procedures not only effect cyclization and aromatization with concomitant loss of water, but also result in demethylation of any pendant methoxy moieties and result in the production of compounds of formula
15 (Ia': A, B, C, D is H or OMe; with the A, B, C, D, combination of substituents having at least one OH group but not more than three OH groups).

In an analogous fashion to the reactions above in Scheme 1B, the compounds of formula (Ia': A is H; B, D is alkyl of 1-6 carbon atoms; C is OH) can be prepared starting from the compound of formula (VIII: Q is H₂) and the appropriate benzoic
20 acid chloride (IX: A is H; B, D is alkyl of 1-6 carbon atoms; C is OMe). The benzoic acid chloride (IX: A is H; B, D is alkyl of 1-6 carbon atoms; C is OMe). is prepared from the corresponding benzoic acid by standard procedures using reagents such as oxalyl chloride and thionyl chloride. The starting benzoic acid of the benzoic acid chloride (IX is H; B, D is alkyl of 1-6 carbon atoms; C is OMe) is commercially
25 available or can be easily prepared by known procedures. For example, the acid starting material for benzoic acid chloride (IX: A is H; B, D is isopropyl; C is OMe) can be prepared using a modification of the method of Schuster, et al., *J. Org. Chem* **1988**, 53, 5819. Thus commercially available 2, 6-diisopropyl phenol is brominated in the 4-position (bromine / acetic acid), methylated (iodomethane / potassium carbonate
30 / DMF), reacted with n-butyl lithium to effect lithium halogen exchange and the

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resultant organolithium species is reacted with carbon dioxide to provide 3, 5-diisopropyl, 4-methoxy benzoic acid.

Scheme 2



5 Further derivatives of the compounds of formula (I) in Scheme 2 can be prepared by the following methods. The phenol of formula (Ib: B, D, X is H; C is OH; E is S, O) can be brominated in three positions to afford the tribromophenol of formula (Ib: B, D, X is Br; C is OH; E is S, O) using at least 3 molar equivalents of molecular bromine in an appropriate solvent such as acetic acid. One to fifty molar

10 equivalents of a salt of acetic acid such as potassium or sodium acetate can also be used as a co-reagent in this reaction although it is not absolutely required. The tribromophenol of formula (Ib: B, D, X is Br; C is OH; E is S, O) can be methylated to produce the methyl ether of formula (Ib: B, D, X is Br; C is OMe; E is S, O) by reacting the phenol moiety with a suitable methylating agent such as one or more

15 molar equivalents of methyl iodide or dimethylsulfate employing a base such as an alkali methyl carbonate or hydroxide such as potassium carbonate or sodium hydroxide in a suitable solvent such as THF, DMF or DMSO. The reaction is generally performed at temperatures ranging from 0°C to 60°C.

The methyl ether of formula (Ib: B, D, X is Br; C is OMe; E is S, O) can be

20 reacted with three or more molar equivalents of lower tetra-alkyltin in the presence of a palladium catalyst such as 1 to 10 mole % of bis(triphenylphosphine)palladium II chloride in a suitable solvent such as DMF, DMA or 1-methyl-2-pyrrolidinone at

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temperatures ranging from 140°C to 200°C to provide the trialkylmethoxy derivative of formula (Ib: B, D, X is alkyl of 1-6 carbon atoms; C is OMe; E is S, O). This methoxy analog can be converted to the corresponding phenol analog of formula (Ic: B, D, X is alkyl of 1-6 carbon atoms; E is S, O) using standard demethylation
5 procedures including one or more molar equivalents of boron tribromide or boron trichloride in dichloromethane at -78°C to room temperature; excess neat pyridinium hydrochloride at 190 to 280°C; hydrobromic acid in acetic acid at 0°C to 50°C; excess trimethylsilylbromide or trimethylsilyliodide in dichloromethane, carbon tetrachloride or acetonitrile at -78°C to 50°C; lithium iodide in pyridine or quinoline at
10 temperatures from 100° to 250°C and one or more molar equivalents of ethyl, methyl or isopropyl mercaptan in the presence of one or more molar equivalents of a Lewis acid such as aluminum trichloride or boron trifluoride in a solvent such as dichloromethane at temperatures ranging from -78°C to 50°C.

The phenol of formula (Ib: B, D, X is H; C is OH; E is S, O) (Scheme 2) can
15 be conveniently iodinated to the diiodophenol of formula (Ib: B, D is I; X is H; C is OH; E is S, O) using at least two molar equivalents of iodine in the presence of two or more molar equivalents of an alkali metal hydroxide such as NaOH in an alcohol solvent such as methanol at -20°C to room temperature. Similarly the monoiodophenol (Ib: B is I; X, D is H; C is OH; E is S, O) can be prepared from the
20 phenol of formula (Ib: B, D, X is H; C is OH; E is S, O) (Scheme 2) using one to 1.5 molar equivalents of iodine in the presence of at least one equivalent of an alkali metal hydroxide such as NaOH in an alcohol solvent such as methanol at -20°C to room temperature. Either the monoiodophenol (Ib: B is I; X, D is H; C is OH; E is S, O) or the diiodophenol (Ib: B, D is I; X is H; C is OH; E is S, O) can be converted to
25 the respective methyl ether derivatives of formula (Ib: B is I; X, D is H; C is OMe; E is S, O) or (Ib: B, D is I; X is H; C is OMe; E is S, O) by reacting the phenol moiety with a suitable methylating agent such as one or more molar equivalents of methyl iodide or dimethylsulfate employing a base such as an alkali methyl carbonate or hydroxide such as potassium carbonate or sodium hydroxide in a suitable solvent such

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as THF, DMF or DMSO. The reaction is generally performed at temperatures ranging from 0°C to 60°C.

The monoiodo methylether derivative of formula (Ib: B is I; X, D is H; C is OMe; E is S, O) or the diiodo methylether of formula (Ib: B, D is I; X is H; C is OMe; E is S, O) can be reacted with one or more molar equivalents of copper (I) cyanide for the monoiodo analog or two or more molar equivalents of copper (I) cyanide for the diiodo derivative to produce the monocyanomethyl ether of formula (Ib: B is CN; X, D is H; C is OMe; E is S, O) or the dicyanomethyl ether of formula (Ib: B, D is CN; X is H; C is OMe; E is S, O). The cyanation reaction is generally performed at temperatures ranging from 100°C to 250°C employing polar aprotic solvents such as DMF, 1-methyl-2-pyrrolidinone or HMPA. Quinoline or pyridine can also be used. The mono or dicyano methoxy analogs of formula (Ib: B is CN; D is H or CN; X is H; C is OMe; E is S, O) can be converted to the corresponding mono or dicyano phenol analogs of formula (Ic: B is CN; D is H or CN; X is H; E is S, O) (Scheme 2) using standard demethylation procedures including one or more molar equivalents of boron tribromide or boron trichloride in dichloromethane at -78°C to room temperature; excess neat pyridinium hydrochloride at 190 to 280°C; hydrobromic acid in acetic acid at 0°C to 50°C; excess trimethylsilylbromide or trimethylsilyliodide in dichloromethane, carbon tetrachloride or acetonitrile at -78°C to 50°C; lithium iodide in pyridine or quinoline at temperatures from 100° to 250°C and one or more molar equivalents of ethyl, methyl or isopropyl mercaptan in the presence of one or more molar equivalents of a Lewis acid such as aluminum trichloride or boron trifluoride in a solvent such as dichloromethane at temperatures ranging from -78°C to 50°C.

The monoiodo methylether derivative of formula (Ib: B is I; X, D is H; C is OMe; E is S, O) or the diiodo methylether of formula (Ib: B, D is I; X is H; C is OMe; E is S, O) (Scheme 2) can be reacted with one or more molar equivalents of copper (I) bromide for the monoiodo analog or two or more molar equivalents of copper (I) bromide for the diiodo derivative to produce the monobromo methyl ether of formula (Ib: B is Br; X, D is H; C is OMe; E is S, O) or the dibromo-methyl ether of formula

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(Ib: B, D is Br; X is H; C is OMe; E is S, O). The bromine/iodine exchange reaction is generally performed at temperatures ranging from 100°C to 250°C employing polar aprotic solvents such as DMF, 1-methyl-2-pyrrolidinone or HMPA. Quinoline or pyridine can also be used. The mono or dibromo methoxy analogs of formula (Ib: B is Br; D is H or Br; X is H; C is OMe; E is S, O) can be converted to the corresponding mono or dibromo phenol analogs of formula (Ic: B is Br; D is H or Br; X is H; E is S, O) (Scheme 2) using standard demethylation procedures including one or more molar equivalents of boron tribromide or boron trichloride in dichloromethane at -78°C to room temperature; excess neat pyridinium hydrochloride at 190 to 280°C; hydrobromic acid in acetic acid at 0°C to 50°C; excess trimethylsilylbromide or trimethylsilyliodide in dichloromethane, carbon tetrachloride or acetonitrile at -78°C to 50°C; lithium iodide in pyridine or quinoline at temperatures from 100° to 250°C and one or more molar equivalents of ethyl, methyl or isopropyl mercaptan in the presence of one or more molar equivalents of a Lewis acid such as aluminum trichloride or boron trifluoride in a solvent such as dichloromethane at temperatures ranging from -78°C to 50°C.

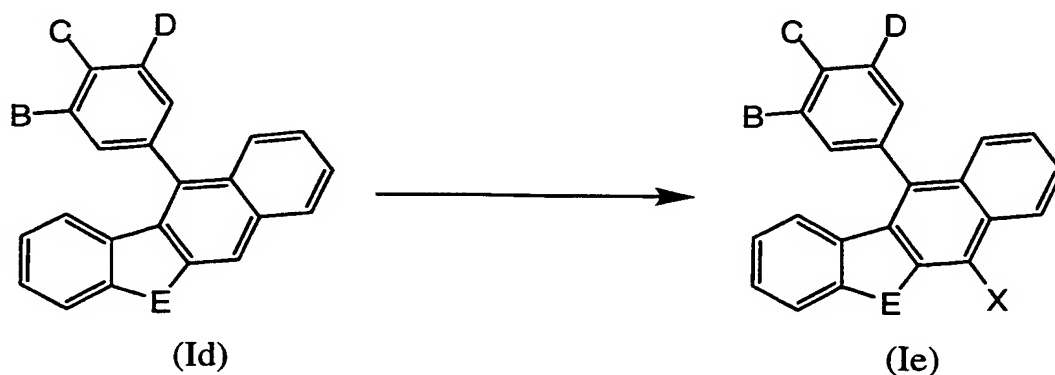
The moniodo or monobromo methylether or phenol derivatives of formula (Ib: B is Br, I; X, D is H; C is , OH, OMe; E is S, O) or the diiodo or dibromo methylether or phenols of formula (Ib: B, D is Br, I; X is H; C is OH, OMe; E is S, O) (Scheme 2) can be reacted with one or more molar equivalents of an aryl boronic acid for the moniodo or monobromo analog or two or more molar equivalents of aryl boronic acid for the diiodo or dbromo derivative to produce the monophenyl methyl ether or phenols of formula (Ib: B is phenyl; X, D is H; C is OH, OMe; E is S, O) or the dibromo-methyl ethers or phenols of formula (Ib: B, D is phenyl; X is H; C is OH, OMe; E is S, O). This reaction is best known as the Suzuki reaction (N. Miyaura, T. Yanagi, A Suzuki, *Synthetic Comm.* **1981**, *11*, 513-319) and further involves the use of 0.5 to 10 mol% of a palladium catalyst such as tetakis(triphenylphosphine) palladium or a palladium (II) species such as palladium acetate or [1,1'-bis(diphenylphosphino)ferrocene]palladium(II). One or more equivalents of an alkali-metal base is also needed and some of the more common bases include sodium,

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potassium or cesium carbonate; sodium, potassium, barium or thallium hydroxide and potassium phosphate. The reaction can be run in a variety of solvents including benzene, THF, dioxane, DME or DMF. For some of these solvents, such as THF and benzene, water or methanol can be used as a colvent. The reaction is generally run at
5 temperatures ranging from room temperature to 120°C.

The mono or dibromo methoxy analogs of formula (Ib: B is Br; D is H or Br; X is H; C is OMe; E is S, O) and the mono and diphenyl methoxy analogs of formula (Ib: B is Ph; D is H or Ph; X is H; C is OMe; E is S, O) can be converted to the corresponding mono or dibromo phenol analogs of formula (Ic: B is Br; D is H or Br; X is H; E is S, O) or the mono and diphenyl phenol analogs of formula (Ib: B is Ph; D is H or Ph; X is H; C is OH; E is S, O) (Scheme 2) using standard demethylation
10 procedures including one or more molar equivalents of boron tribromide or boron trichloride in dichloromethane at -78°C to room temperature; excess neat pyridinium hydrochloride at 190 to 280°C; hydrobromic acid in acetic acid at 0°C to 50°C; excess
15 trimethylsilylbromide or trimethylsilyliodide in dichloromethane, carbon tetrachloride or acetonitrile at -78°C to 50°C; lithium iodide in pyridine or quinoline at temperatures from 100° to 250°C and one or more molar equivalents of ethyl, methyl or isopropyl mercaptan in the presence of one or more molar equivalents of a Lewis
20 acid such as aluminum trichloride or boron trifluoride in a solvent such as dichloromethane at temperatures ranging from -78°C to 50°C.

Scheme 3



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Further derivatives of the compounds of formula (I) in Scheme 3 can be prepared by the following methods. The compounds of formula (Id: B, C, D is H or OH; with the B, C, D combination having at least one OH group; E is S, O) (Scheme 3) can be acylated on the phenolic oxygen using one or more molar equivalents of suitable acylating agent to provide the compounds of formula (Id: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; E is S, O). The acylating agent is generally a alkyl of 1-6 carbon atoms or aryl carboxylic acid anhydride or a alkyl of 1-6 carbon atoms or aryl carboxylic acid chloride. The reaction is run under standard conditions, for example, the use of pyridine as solvent with or without a co-solvent such as dichloromethane at 0°C to room temperature. The acylated phenols of formula (Id: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) can then be brominated in the 6-position of the benzo[b]naphtho[2,3-d]thiophene or benzo[b]naphtho[2,3-d]furan ring to form the acylated bromophenols of formula (Ie: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; X is Br; E is S, O) (Scheme 3). This bromination reaction is generally done using 1 to 1.3 molar equivalents of molecular bromine in an inert solvent such as dichloromethane or carbon tetrachloride at temperatures ranging from -78 °C to room temperature.

Using a similar bromination reaction, the phenols of formula (Id: B, D is alkyl of 1-6 carbon atoms, C is OH; E is S, O) can then be brominated in the 6-position of the benzo[b]naphtho[2,3-d]thiophene or benzo[b]naphtho[2,3-d]furan ring to form the bromophenols of formula (Ie: B, D is alkyl of 1-6 carbon atoms, C is OH; X is Br; E is S, O) (Scheme 3). This bromination reaction is generally done using 1 to 1.3 molar equivalents of molecular bromine in an inert solvent such as dichloromethane or carbon tetrachloride at temperatures ranging from -78 °C to room temperature.

The acyl group can then be removed from the acylated bromophenols of formula (Ie: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; X is Br; E is S, O) to provide the

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bromophenols of formula (Ie: B, C, D is H or OH; with the B, C, D combination having at least one OH group; X is Br; E is S, O) (Scheme 3) using standard conditions. These conditions include aqueous base in which one or more molar equivalents of alkali metal hydroxide such as sodium hydroxide is used in water with
5 a co-solvent such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol at temperatures ranging from 0°C to 40°C. acid conditions may also be employed in which the compound is reacted with one or more molar equivalents of a mineral acid such as HCl or sulfuric acid in water with or without a co-solvent such as THF at temperatures ranging from room temperature to
10 80°C.

The acylated phenols of formula (Id: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) can be nitrated to provide the nitro compounds of formula (Ie: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of
15 1-6 carbon atoms, aryl; X is NO₂; E is S, O) (Scheme 3). Dilute nitric acid at temperatures ranging from 0°C to room temperature is suitable to effect this transformation. The nitro compounds of formula (Ie: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; X is NO₂; E is S, O) can be further reduced to the primary amine of formula (Ie:
20 B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; X is NH₂; E is S, O) using a suitable reducing agent such as catalytic hydrogenation with a palladium or platinum catalyst, tin dichloride in aqueous HCl or in ethyl acetate. The acyl group of the compounds of formula (Ie: B, C, D is H or OCOR; with the B, C, D combination having at least one
25 OCOR group; R is alkyl of 1-6 carbon atoms, aryl; X is NO₂ or NH₂; E is S, O) can be removed by using standard conditions to provide the phenols of formula (Ie: B, C, D is H or OH; with the B, C, D combination having at least one OH group; R is alkyl of 1-6 carbon atoms, aryl; X is NO₂ or NH₂; E is S, O).

The acylated bromophenols of formula (Ie: B, C, D is H or OCOR; with the B,
30 C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms,

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aryl; X is Br; E is S, O) (Scheme 3) can be converted to the acylated cyanophenols of formula (Ie: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; X is CN; E is S, O) by reaction with one or more molar equivalents of copper (I) cyanide. The cyanation reaction is generally performed at temperatures ranging from 100°C to 250°C employing polar aprotic solvents such as DMF, 1-methyl-2-pyrrolidinone or HMPA. Quinoline or pyridine can also be used. Often the acyl group of (Ie: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; X is CN; E is S, O) is liberated under the cyanation reaction conditions to afford the cyanophenols of formula (Ie: B, C, D is H or OH; with the B, C, D combination having at least one OCOR group; X is CN; E is S, O). This liberation of the acyl group to afford the cyanophenols of formula (Ie: B, C, D is H or OH; with the B, C, D combination having at least one OH group; X is CN; E is S, O) can be effected most readily by addition of one or more molar equivalents of alkali metal hydroxide in water to the reaction mixture containing (Ie: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; X is CN; E is S, O) prior to workup. The acyl group can also be removed from the isolated acylated cyanophenols of formula (Ie: B, C, D is H or OCOR; with the B, C, D combination having at least one OCOR group; R is alkyl of 1-6 carbon atoms, aryl; X is CN; E is S, O) to provide the cyanophenols of formula (Ie: B, C, D is H or OH; with the B, C, D combination having at least one OH group; X is CN; E is S, O) by using standard conditions. These conditions include aqueous base in which one or more molar equivalents of alkali metal hydroxide such as sodium hydroxide is used in water with a co-solvent such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol at temperatures ranging from 0°C to 40°C. acid conditions may also be employed in which the compound is reacted with one or more molar equivalents of a mineral acid such as HCl or sulfuric acid in water with or without a co-solvent such as THF at temperatures ranging from room temperature to 80°C.

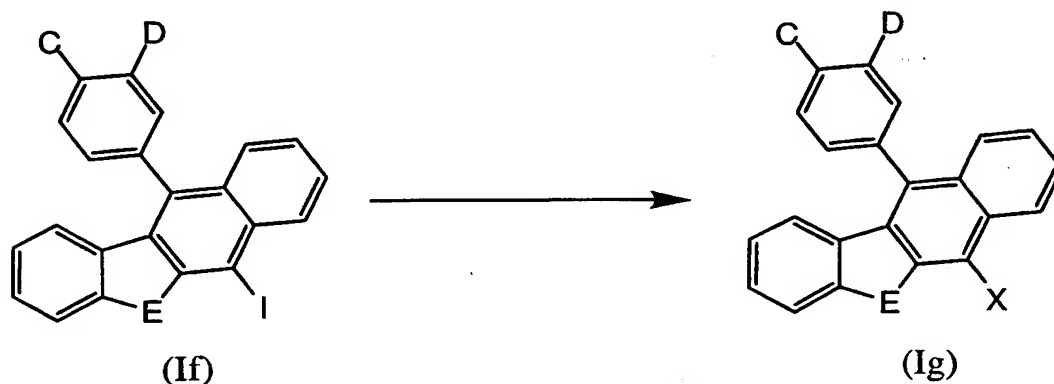
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The compounds of formula (Id: B, C, D is H or OH; with the B, C, D combination having at least one OH group; E is S, O) (Scheme 3) can be sulfonylated on the phenolic oxygen using one or more molar equivalents of suitable sulfonylating agent to provide the sulfonic acid esters of formula (Id: B, C, D is H or OSO₂R; with the B, C, D combination having at least one OSO₂R group; R is alkyl of 1-6 carbon atoms, aryl; E is S, O). The sulfonylating agent is generally a alkyl of 1-6 carbon atoms or aryl sulfonic acid anhydride or a alkyl of 1-6 carbon atoms or aryl sulfonic acid chloride. The reaction is run under standard conditions such as using pyridine as solvent with or without a co-solvent such as dichloromethane at 0°C to room temperature.

The sulfonic acid esters of formula (Id: B, C, D is H or OSO₂R; with the B, C, D combination having at least one OSO₂R group; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) can be treated with a chlorinating agent to effect chlorination at the 6-position of the benzo[b]naphtho[2,3-d]thiophene or benzo[b]naphtho[2,3-d]furan ring to afford the chloro-sulfonic acid esters of formula (Ie: B, C, D is H or OSO₂R; with the B, C, D combination having at least one OSO₂R group; R is alkyl of 1-6 carbon atoms, aryl; X is Cl; E is S, O). Suitable chlorinating agents include one or more molar equivalents of sulfuryl chloride, chlorine gas or N-chlorosuccinimide in suitable halocarbon solvents such as dichloromethane or chloroform at temperatures ranging from -78°C to 40 °C. The sulfonic ester group can then be removed from the chloro-sulfonic acid esters of formula (Ie: B, C, D is H or OSO₂R; with the B, C, D combination having at least one OSO₂R group; R is alkyl of 1-6 carbon atoms, aryl; X is Cl; E is S, O) to provide the chlorophenols of formula (Ie: B, C, D is H or OH; with the B, C, D combination having at least one OH group; X is Cl; E is S, O) (Scheme 3) using standard conditions. These conditions include aqueous base in which one or more molar equivalents of alkali metal hydroxide such as sodium hydroxide is used in water with a co-solvent such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol at temperatures ranging from room temperature to 110°C.

The sulfonic acid esters of formula (Id: B, C, D is H or OSO₂R; with the B, C, D combination having at least one OSO₂R group; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) can also be treated with iodinating reagents to effect iodination at the 6-position of the benzo[b]naphtho[2,3-d]thiophene or benzo[b]naphtho[2,3-d]furan ring to afford the iodo-sulfonic acid esters of formula (Ie: B, C, D is H or OSO₂R; with the B, C, D combination having at least one OSO₂R group; R is alkyl of 1-6 carbon atoms, aryl; X is I; E is S, O). A suitable iodinating reagent includes a mixture of 0.7 or more molar equivalents of molecular iodine and 0.25 or more molar equivalents of iodic acid in a mixture of THF and 80% aqueous acetic acid with a small amount of concentrated sulfuric acid at temperatures ranging from room temperature to 80°C. The sulfonic ester group can then be removed from the iodo-sulfonic acid esters of formula (Ie: B, C, D is H or OSO₂R; with the B, C, D combination having at least one OSO₂R group; R is alkyl of 1-6 carbon atoms, aryl; X is I; E is S, O) to provide the iodophenols of formula (Ie: B, C, D is H or OH; with the B, C, D combination having at least one OH group; X is I; E is S, O) (Scheme 3) using standard conditions. These conditions include aqueous base in which one or more molar equivalents of alkali metal hydroxide such as sodium hydroxide is used in water with a co-solvent such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol at temperatures ranging from room temperature to 110°C.

Scheme 4



The iodo sulfonic acid esters of formula (If: C, D is H or OSO₂R; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) were a convenient starting

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point for further derivatives of the compounds of formula (I) as shown in Scheme 4 and the methods below. The compounds (If: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) can be reacted with a reagent that catalyzes the exchange of the iodine atom in (If) with a perfluoroalkyl of 1-6 carbon atoms group to afford the compound of formula (Ig: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; X is perfluoroalkyl of 1-6 carbon atoms; E is S, O) (Scheme 4). The reagent and conditions to effect this exchange include reacting (If) under anhydrous conditions with one to ten molar molar equivalents of a sodium perfluorocarboxylate (RCO_2Na : R is perfluoroalkyl) and one to five molar molar equivalents of copper (I) iodide in a high boiling inert solvent such as DMF, DMA or 1-methyl-2-pyrrolidinone at temperatures ranging from 140°C to 200°C . Alternatively, the compound of formula (Ig: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; X is perfluoroalkyl of 1-6 carbon atoms; E is S, O) can be prepared from the compound of formula (If: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) by reacting the former with one to ten molar molar equivalents of a perfluoroalkyl iodide and one to five molar molar equivalents of activated Cu^0 in a high boiling inert solvent such as DMF, DMA or 1-methyl-2-pyrrolidinone at temperatures ranging from 140°C to 200°C . Still, alternatively, the compound of formula (If: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) can be reacted with 0.5 to two molar equivalents of bis(trifluoromethylmercury) and two to four molar equivalents of activated Cu^0 in a high boiling inert solvent such as DMF, DMA or 1-methyl-2-pyrrolidinone at temperatures ranging from 140°C to 200°C to produce the compound of (Ig: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; X is CF_3 ; E is S, O).

6-Alkyl of 1-6 carbon atoms derivatives of the compound of formula (Ig: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; X is alkyl of 1-6 carbon atoms; E is S, O) (Scheme 4) can be prepared by reaction of (If: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) with three or more molar equivalents of lower tetra-alkyltin in the presence of a

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palladium catalyst such as 1 to 10 mole % of bis(triphenylphosphine)palladium II chloride in a suitable solvent such as DMF, DMA or 1-methyl-2-pyrrolidinone at temperatures ranging from 140°C to 200°C.

The sulfonic ester group can then be removed from the sulfonic acid esters of formula (Ig: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; X is alkyl of 1-6 carbon atoms or perfluoroalkyl of 1-6 carbon atoms; E is S, O) to provide the phenols of formula (Ig: C, D is H or OH; C, D cannot both be H; X is alkyl of 1-6 carbon atoms or perfluoroalkyl of 1-6 carbon atoms; E is S, O) using standard conditions. These conditions include aqueous base in which one or more molar equivalents of alkali metal hydroxide such as sodium hydroxide is used in water with a co-solvent such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol at temperatures ranging from room temperature to 110°C.

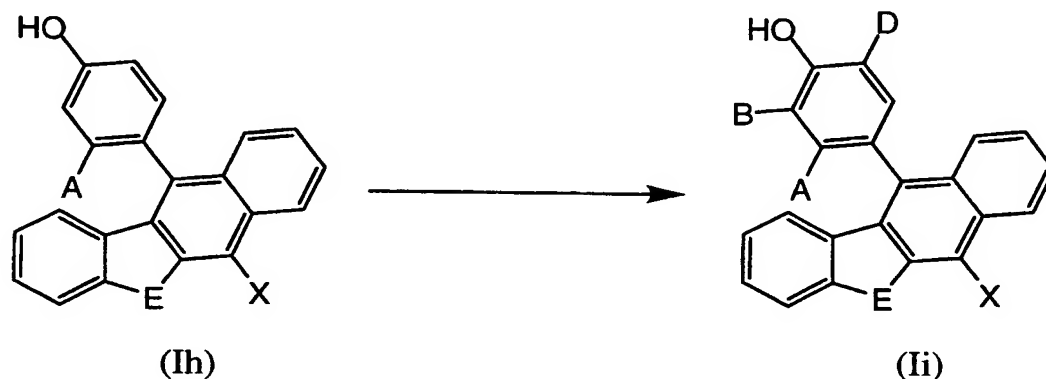
6-Alkoxy derivatives of the compound of formula (Ig: C, D is H, OH; C, D cannot both be H; X is alkoxy of 1-6 carbon atoms; E is S, O) can be prepared by reaction of (If: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) with three or more molar equivalents of lower alkali metal alkoxide in the presence of a copper (I) or copper (II) catalyst such as 1 to 10 mole % copper (II) chloride in a suitable solvent such as DMF, DMA or 1-methyl-2-pyrrolidinone at temperatures ranging from 80°C to 180°C. Under the reaction conditions, the sulfonic acid group of (If: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) is removed.

6-Sulfanyl derivatives of the compound of formula (Ig: C, D is H or OH; C, D cannot both be H; X is alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can be prepared by reaction of (If: C, D is H or OSO_2R ; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) with one or more molar equivalents of the appropriate alkyl of 1-6 carbon atomsthiol, arylthiol, thiopyridine or 2-N,N-dimethylaminoethyl-mercaptan, one or more molar equivalents of an alkali metal hydroxide such as sodium hydroxide, one or more molar equivalents of a copper (I) or copper (II)

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catalyst such as copper (I) oxide in a suitable solvent such as DMF, DMA or 1-methyl-2-pyrrolidinone at temperatures ranging from 100°C to 180°C. Under the reaction conditions, the sulfonic acid group of (If: C, D is H or OSO₂R; C, D cannot both be H; R is alkyl of 1-6 carbon atoms, aryl; E is S, O) is removed.

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Scheme 5

Further derivatives of the compounds of formula (I) in Scheme 5 can be prepared by the following methods. The phenols of formula (Ih: A is H or OH; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can be brominated in two positions to afford the dibromophenols of formula (Ii: A is H or OH; B, D is Br; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) using at least 2 molar equivalents of molecular bromine in an appropriate solvent such as acetic acid. One to fifty molar equivalents of a salt of acetic acid such as potassium or sodium acetate can also be used as a co-reagent in this reaction although it is not absolutely required.

The phenols of formula (Ih: A is H or OH; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-

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N,N-dimethylaminoethylsulfanyl; E is S, O) can be chlorinated in two positions to afford the dichlorophenols of formula (Ii: A is H or OH; B, D is Cl; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) using two or more molar equivalents of chlorine in an appropriate solvent such as a lower alcohol solvent, most conveniently, methanol. The reaction is run at temperatures ranging from -78°C to room temperature.

The phenols of formula (Ih: A is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can be mononitrated to the phenols of formula (Ii: A is H; B is NO₂; D is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) most conveniently using iron (III) trinitrate in a lower alcohol solvent.

The nitro compounds of formula (Ii: A is H; B is NO₂; D is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be reduced to the amino compounds of formula (Ii: A is H; B is NH₂; D is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, amino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) most readily using tin dichloride in ethyl acetate at 40 to 100°C or with hydrazine and Montmorillonite clay in ethanol at 40 to 100°C.

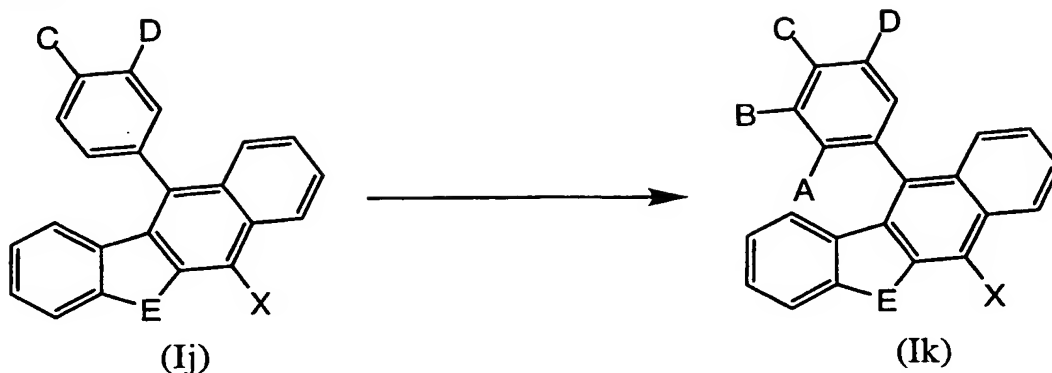
The nitro compounds of formula (Ii: A is H; B is NO₂; D is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl,

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pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can also be brominated to the compounds of formula (Ii: A is H; B is NO₂; D is Br; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) using at least 2 molar equivalents of molecular bromine in an appropriate solvent such as acetic acid. One to fifty molar equivalents of a salt of acetic acid such as potassium or sodium acetate can also be used as a co-reagent in this reaction although it is not absolutely required. The bromo nitro compounds of formula (Ii: A is H; B is NO₂; D is Br; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can be reduced to the bromo amino compounds of formula (Ii: A is H; B is NH₂; D is Br; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, amino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) most readily using tin dichloride in ethyl acetate at 40 to 100°C or with hydrazine and Montmorillinite clay in ethanol at 40 to 100°C.

The dibromo-bisphenols of formula (Ii: A is OH; B, D is Br; X is H; E is S, O) can be further brominated in the 6-position of the benzo[b]naphtho[2,3-d]thiophene ring to form the bisphenols of formula (Ii: A is OH; B, D, X is Br; E is S, O). This bromination reaction is generally done using 1 to 1.3 molar equivalents of molecular bromine in an inert solvent such as dichloromethane or carbon tetrachloride at temperatures ranging from -78 °C to room temperature.

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Scheme 6

Further derivatives of the compounds of formula (I) in Scheme 6 can be prepared by the following methods. The phenols of formula (Ij: C is H; D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can be mono-brominated to provide the provide the bromophenols of formula (Ik: A, B is H; C is Br; D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) using at least 1 molar equivalent of molecular bromine in an appropriate solvent such as acetic acid or dibrominated to provide the bromophenols of formula (Ik: B is H; A, C is Br; D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) using at least 2 molar equivalents of molecular bromine in an appropriate solvent such as acetic acid. Similarly, the bisphenols of formula (Ij: C, D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can be monobrominated to provide a mixture of the bromobisphenols of formula (Ik: A is H; B is Br; C, D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6

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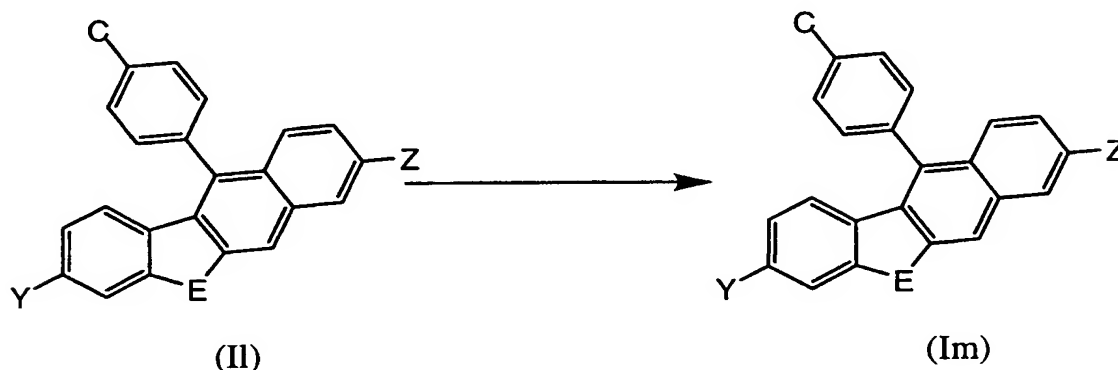
carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) and (Ik: A is Br; B is H; C, D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethyl-
5 amino-ethylsulfanyl; E is S, O) using at 1 molar equivalent of molecular bromine in an appropriate solvent such as acetic acid. This mixture can be separated into pure monobromo products by conventional means.

The bromobisphenols of formula (Ik: A is H; B is Br; C, D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy
10 of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be alkylated regioselectively with a alkyl of 1-6 carbon atoms, allyl or benzyl halide on the phenolic hydroxyl occupied by position C to provide the monoalkylated products of formula (Ik: A is H; B is Br; C is alkoxy of 1-6 carbon atoms, allyloxy or benzyloxy,
15 D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) using one or more molar equivalents of an alkali metal carbonate such as potassium carbonate in a polar aprotic solvent such as DMF.

20 The monobenzylated products of formula (Ik: A is H; B is Br; C is benzyloxy, D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be further alkylated with a alkyl of 1-6 carbon atoms halide to provide the dialkylated
25 product of formula (Ik: A is H; B is Br; C is benzyloxy, D is alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) using one or more molar equivalents of an alkali metal carbonate such as potassium
30 carbonate in a polar aprotic solvent such as DMF.

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The benzyl group of the compounds of formula (Ik: A is H; B is Br; C is benzyloxy, D is alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be removed using standard
 5 hydrogenolysis conditions, for example, hydrogen gas with a 5 to 10% palladium on carbon catalyst in a lower alcohol solvent or in ethyl acetate or THF to provide the phenols of formula (Ik: A is H; B is Br; C is OH, D is alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy
 10 of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O).

Scheme 7

Further derivatives of the compounds of formula (I) in Scheme 7 can be prepared by the following methods. The bisphenol of formula (II: Y, C is OH; Z is H; E is S) can be reacted with one molar equivalent of methyl bromoacetate and with one
 15 or more molar equivalents of an alkali metal carbonate such as potassium carbonate in a polar aprotic solvent such as DMF to afford the monoalkylated product of formula (Im: Y is OCH₂CO₂CH₃; C is OH; Z is H; E is S). This product may be contaminated with small amounts (<10%) of the regioisomer of formula (Im: C is OCH₂CO₂CH₃; Y
 20 is OH; Z is H; E is S). The regioisomers can be separated by conventional means.

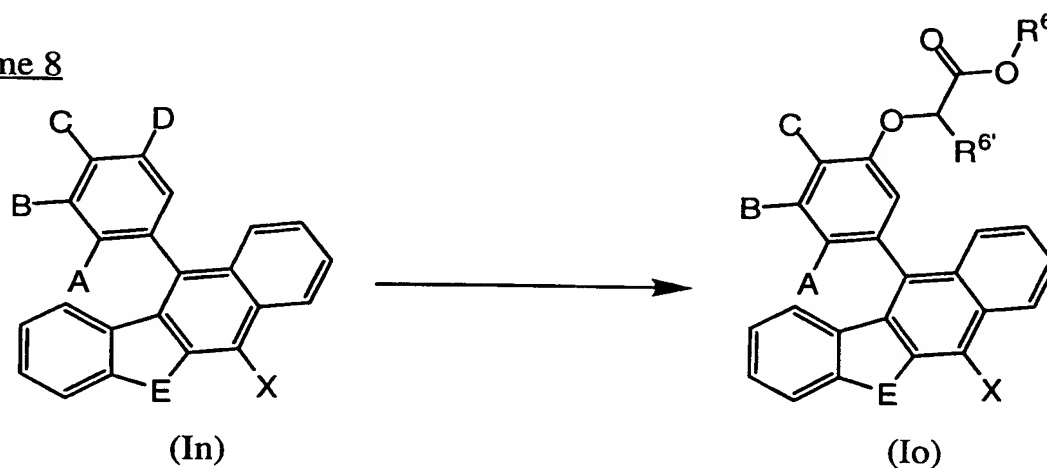
Alternatively, the bisphenols of formula (II: Y, C is OH; Z is H; E is S) or (Z, C is OH; Y is H; E is S or O) can be dialkylated with two or more molar equivalents of an alkyl haloacetate of formula (X²CH₂CO₂R⁶ where X² is Cl, Br or I and R⁶ is

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alkyl of 1-6 carbon atoms) and with two or more molar equivalents of an alkali metal carbonate such as potassium carbonate in a polar aprotic solvent such as DMF to afford the dialkylated product of formula (Im: Y, C is $\text{OCH}_2\text{CO}_2\text{R}^6$; Z is H; E is S; R^6 is alkyl of 1-6 carbon atoms) or (Z, C is $\text{OCH}_2\text{CO}_2\text{R}^6$; Y is H; E is S or O; R^6 is alkyl of 1-6 carbon atoms).

The monoesters of formula (Im: Y is $\text{OCH}_2\text{CO}_2\text{CH}_3$; C is OH; Z is H; E is S) as well as the diesters of formula (Im: Y, C is $\text{OCH}_2\text{CO}_2\text{R}^6$; Z is H; E is S; E is S) or (Z, C is $\text{OCH}_2\text{CO}_2\text{R}^6$; Y is H; E is S or O) can be transformed into their carboxylic acid analogs using standard conditions to afford the monocarboxylic acids of formula (Im: Y is $\text{OCH}_2\text{CO}_2\text{H}$; C is OH; Z is H; E is S) and the dicarboxylic acids of formula (Im: Y, C is $\text{OCH}_2\text{CO}_2\text{H}$; Z is H; E is S) or (Z, C is $\text{OCH}_2\text{CO}_2\text{H}$; Y is H; E is S or O). The conditions to effect these transformations include aqueous base in which one or more molar equivalents of alkali metal hydroxide such as sodium hydroxide is used in water with a co-solvent such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol at temperatures ranging from 0°C to 40°C .

Scheme 8



Further derivatives of the compounds of formula (I) in Scheme 8 can be prepared by the following methods. The phenols of formula (In: B is H; A, C is H, Br or alkoxy of 1-6 carbon atoms; D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethyl-aminoethylsulfanyl; E is S, O) can be alkylated with one or more molar equivalents of

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an alkyl haloacetate of formula ($X^2CHR^6CO_2R^6$ where X^2 is Cl, Br or I and R^6 is alkyl of 1-6 carbon atoms, R^6 is H) and with one or more molar equivalents of an alkali metal carbonate such as potassium carbonate in a polar aprotic solvent such as DMF to afford the alkylated product of formula (Io: B is H; A, C is H, Br or alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; R^6 is alkyl of 1-6 carbon atoms, R^6 is H; E is S, O).

Alternatively the bisphenols of formula (In: A, B is H or Br; C, D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can be dialkylated with two or more molar equivalents of an alkyl haloacetate of formula ($X^2CHR^6CO_2R^6$ where X^2 is Cl, Br or I and R^6 is alkyl of 1-6 carbon atoms, R^6 is H) and with two or more molar equivalents of an alkali metal carbonate such as potassium carbonate in a polar aprotic solvent such as DMF to afford the dialkylated esters of formula (Io: A, B is H or Br; C is $OCHR^6CO_2R^6$; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R^6 is alkyl of 1-6 carbon atoms, R^6 is H; E is S, O).

Still alternatively, the phenols of formula (In: B is H or halogen; A is H or halogen; C is H, Br or alkoxy of 1-6 carbon atoms; D is OH; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can be reacted with a 2-hydroxy carboxylic acid ester of formula $CH(OH)(R^6)CO_2R^6$ (R^6 , R^6 is alkyl of 1-6 carbon atoms, aralkyl, aryl) to afford the esters of formula (Io: B is H or halogen; A is H or halogen; C is H, Br or alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy,

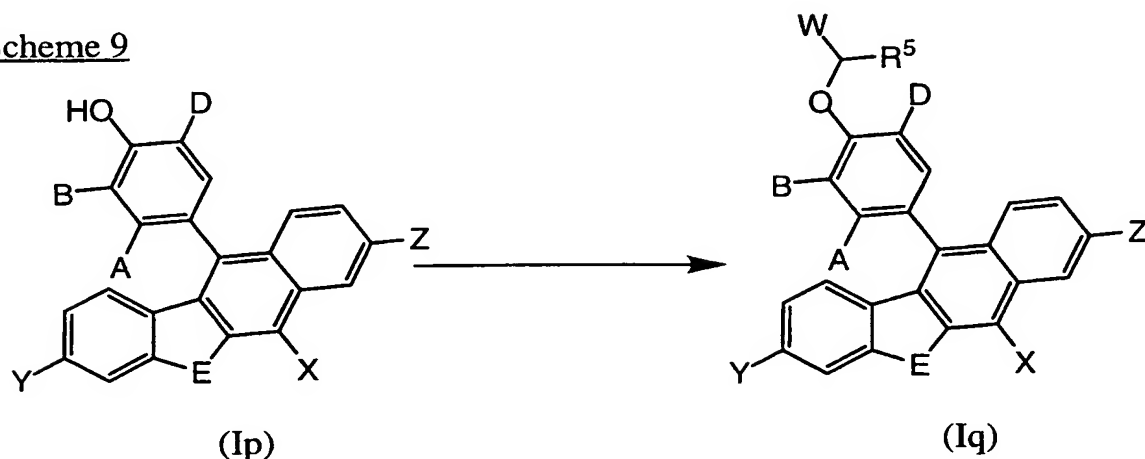
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- nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; R^6 , $R^{6'}$ is alkyl of 1-6 carbon atoms, aralkyl, aryl; E is S, O) under the conditions of the Mitsunobu Reactions (for a review see Oyo Mitsunobu *Synthesis*. **1981**, 1-27). The other co-reagents necessary to effect the Mitsunobu
- 5 Reaction include one or more molar equivalents of a alkyl of 1-6 carbon atoms azodicarboxylate diester such as diethyl azodicarboxylate or diisopropyl azodicarboxylate and one or more molar equivalents of triarylphosphine such as triphenylphosphine in a suitable solvent such as diethyl ether, THF, benzene or toluene at temperatures ranging from -20°C to 120°C .
- 10 The monoesters of formula (Io: A, B is H or halogen; C is H, Br or alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; R^6 , $R^{6'}$ is alkyl of 1-6 carbon atoms, aralkyl, aryl; E is S, O) as well as the diesters of
- 15 formula (Io: A, B is H or Br; C is $\text{OCHR}^6\text{CO}_2\text{R}^6$, X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R^6 is alkyl of 1-6 carbon atoms, $R^{6'}$ is H; E is S, O) can be transformed into their carboxylic acid analogs using standard conditions to afford
- 20 the monocarboxylic acids of formula (Io: A, B is H or halogen; C is H, Br or alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; R^6 is H; $R^{6'}$ is alkyl of 1-6 carbon atoms, aralkyl, aryl; E is S, O) and the dicarboxylic acids
- 25 of formula (Io: A, B is H or Br; C is $\text{OCHR}^6\text{CO}_2\text{R}^6$, X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R^6 , $R^{6'}$ is H; E is S, O). The conditions to effect these transformations include aqueous base in which one or more molar equivalents of
- 30 alkali metal hydroxide such as sodium hydroxide is used in water with a co-solvent

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such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol at temperatures ranging from 0°C to 40°C.

Scheme 9



- Further derivatives of the compounds of formula (I) in Scheme 9 can be prepared by the following methods. The phenols of formula (Ip: A is H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or OCH₂CO₂R⁶, but Y and Z are not concurrently OCH₂CO₂R⁶; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R⁶ is alkyl of 1-6 carbon atoms; E is S, O) can be alkylated with one or more molar equivalents of an alkyl haloacetate of formula (X²CH₂CO₂R⁶ where X² is Cl, Br or I and R⁶ is alkyl of 1-6 carbon atoms) and with one or more molar equivalents of an alkali metal carbonate such as potassium carbonate in a polar aprotic solvent such as DMF to afford the alkylated product of formula (Iq: A is H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or OCH₂CO₂R⁶, but Y and Z are not concurrently OCH₂CO₂R⁶; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CO₂R⁶; R⁵ is H; R⁶ is alkyl of 1-6 carbon atoms; E is S, O).

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The phenols of formula (Ip: A is H or OH; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or $\text{OCH}_2\text{CO}_2\text{R}^6$, but Y and Z are not concurrently $\text{OCH}_2\text{CO}_2\text{R}^6$; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R^6 is alkyl of 1-6 carbon atoms; E is S, O) can be reacted with a 2-hydroxy carboxylic acid ester of formula $\text{CH}(\text{OH})(\text{R}^5)\text{CO}_2\text{R}^6$ (R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $\text{CH}_2(3\text{-1H-indolyl})$, $\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2(3\text{-pyridyl})$, $\text{CH}_2\text{CO}_2\text{R}^6$, R^6 is alkyl of 1-6 carbon atoms) to afford the esters of formula (Iq: A is H or OH; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or $\text{OCH}_2\text{CO}_2\text{R}^6$, but Y and Z are not concurrently $\text{OCH}_2\text{CO}_2\text{R}^6$; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CO_2R^6 ; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $\text{CH}_2(3\text{-1H-indolyl})$, $\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2(3\text{-pyridyl})$, $\text{CH}_2\text{CO}_2\text{R}^6$, R^6 is alkyl of 1-6 carbon atoms; E is S, O) under the conditions of the Mitsunobu Reactions (for a review see Oyo Mitsunobu *Synthesis*. **1981**, 1-27). The other co-reagents necessary to effect the Mitsunobu Reaction include one or more molar equivalents of a alkyl of 1-6 carbon atoms azodicarboxylate diester such as diethyl azodicarboxylate or diisopropyl azodicarboxylate and one or more molar equivalents of triarylphosphine such as triphenylphosphine in a suitable solvent such as diethyl ether, THF, benzene or toluene at temperatures ranging from -20°C to 120°C .

The 2-hydroxy carboxylic acid ester of formula $\text{CH}(\text{OH})(\text{R}^5)\text{CO}_2\text{R}^6$ (R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $\text{CH}_2(3\text{-1H-indolyl})$, $\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2(3\text{-pyridyl})$, $\text{CH}_2\text{CO}_2\text{R}^6$, R^6 is alkyl of 1-6 carbon atoms) are

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commercially available or can be prepared from commercially available carboxylic acid precursors under standard esterification conditions. (S)-(+)-2-Hydroxy-1-oxo-3-dihydro-2-isoindolinebutyric acid, methyl ester can be prepared from (S)-(+)-2-hydroxy-1,3-dioxo-2-isoindolinebutyric acid, methyl ester via sequential treatment
5 with 1) sodium borohydride in THF-water; 2) trifluoroacetic acid / chloroform; 3) triethylsilane / trifluoroacetic acid and 4) aqueous sodium bicarbonate.

3-(Pyridin-3-yl)-phenyllactic acid, ethyl ester can be prepared according to the two step procedure of B.A. Lefker, W.A. Hada, P.J. McGarry *Tetrahedron Lett.* **1994**, *35*, 5205-5208, from commercially available 3-pyridinecarboxaldehyde and ethyl
10 chloroacetate.

The esters of formula (Iq: A is H; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl; W is CO₂tBu; R⁵ is
15 H; E is S, O) can be treated with one or more molar equivalents of a strong base such as lithium diisopropyl amide in a suitable solvent such as THF at temperatures ranging from -78°C to room temperature. This procedure produces an anion alpha to the ester carbonyl. The resultant anion is treated with one or more molar equivalents of an alkyl halide of formula X²R⁵ (where X² is halogen; R⁵ is alkyl and aralkyl) and
20 warmed to room temperature to produce the alkylated ester of formula (Iq: A is H; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl alkoxy of 1-6 carbon atoms; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl; W is CO₂tBu; R⁵ is alkyl and aralkyl; E is S, O).

25 The esters of formula (Iq: A is H or OH; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or OCH₂CO₂R⁶, but Y and Z are not concurrently OCH₂CO₂R⁶; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CO₂R⁶; R⁵ is H, alkyl of 1-
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6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $\text{CH}_2(3\text{-1H-indolyl})$, $\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2(3\text{-pyridyl})$, $\text{CH}_2\text{CO}_2\text{R}^6$, R^6 is alkyl of 1-6 carbon atoms; E is S, O) can be transformed into their carboxylic acid analogs using standard conditions to afford the

5 carboxylic acids of formula (Iq): A is H or OH; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or $\text{OCH}_2\text{CO}_2\text{H}$, but Y and Z are not concurrently $\text{OCH}_2\text{CO}_2\text{H}$; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-

10 dimethylamino-ethylsulfanyl; W is CO_2H ; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $\text{CH}_2(3\text{-1H-indolyl})$, $\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2(3\text{-pyridyl})$, $\text{CH}_2\text{CO}_2\text{H}$; E is S, O). The conditions to effect these transformations include aqueous base in which one or more molar equivalents of alkali metal hydroxide such as sodium

15 hydroxide is used in water with a co-solvent such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol at temperatures ranging from 0°C to 40°C . Alternatively, acid conditions may also be employed in which the above mentioned carboxylic acid ester of formula (Iq) is reacted with one or more molar equivalents of a mineral acid such as HCl or sulfuric acid in water with or

20 without a co-solvent such as THF at temperatures ranging from room temperature to 80°C . Still alternatively, many other conditions may be employed to effect the above mentioned ester to acid transformation leading to (Iq). These include reacting the carboxylic acid ester of formula (Iq) with one or more molar equivalents of boron tribromide or boron trichloride in dichloromethane at -78°C to room temperature; one

25 or more molar equivalents hydrobromic acid in acetic acid at 0°C to 50°C ; one or more molar equivalents trimethylsilylbromide or trimethylsilyliodide in dichloromethane, carbon tetrachloride or acetonitrile at -78°C to 50°C ; one or more molar equivalents lithium iodide in pyridine or quinoline at temperatures from 100° to 250°C .

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When the esters of formula (Iq: A is H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is Br or I; W is CO_2R^6 ; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH_2 (1H-imidazol-4-yl), CH_2 (3-1H-indolyl), CH_2CH_2 (1,3-dioxo-1,3-dihydro-isoindol-2-yl), CH_2CH_2 (1-oxo-1,3-dihydro-isoindol-2-yl), CH_2 (3-pyridyl), $\text{CH}_2\text{CO}_2\text{R}^6$, R^6 is alkyl of 1-6 carbon atoms; E is S, O) are reacted with two or more molar equivalents of trimethylsilyliodide in dichloromethane at temperatures ranging from 0°C to room temperature, conversion to the carboxylic acids takes place (i.e., W is CO_2H) but also the 6-halogen (X is Br or I) is reduced to give the carboxylic acids of formula (Iq: A is H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H; W is CO_2H ; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH_2 (1H-imidazol-4-yl), CH_2 (3-1H-indolyl), CH_2CH_2 (1,3-dioxo-1,3-dihydro-isoindol-2-yl), CH_2CH_2 (1-oxo-1,3-dihydro-isoindol-2-yl), CH_2 (3-pyridyl), $\text{CH}_2\text{CO}_2\text{H}$; E is S, O).

15 The phenols of formula (Ip: A is H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or $\text{OCH}_2\text{CO}_2\text{R}^6$, but Y and Z are not concurrently $\text{OCH}_2\text{C}_2\text{R}^6$; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R^6 is alkyl of 1-6 carbon atoms; E is S, O) can be alkylated with one or more molar equivalents of diethyl trifluoromethylsulfonyloxymethylphosphanate (D.P. Phillion and S.S. Andrew *Tet. Lett.* **1986**, 1477-1480) and with one or more molar equivalents of an alkali metal hydride such as sodium hydride in a suitable solvent such as THF or DMF to afford the diethylphosphonate product of formula (Iq: A is H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or $\text{OCH}_2\text{CO}_2\text{R}^6$, but Y and Z are not concurrently $\text{OCH}_2\text{CO}_2\text{R}^6$; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridyl-

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sulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is PO_3Et_2 ; R^5 is H; R^6 is alkyl of 1-6 carbon atoms; E is S, O).

The phenols of formula (Ip: A is H or OH; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or
5 $\text{OCH}_2\text{CO}_2\text{R}^6$, but Y and Z are not concurrently $\text{OCH}_2\text{CO}_2\text{R}^6$; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R^6 is alkyl of 1-6 carbon atoms; E is S, O) can be reacted with a 2-hydroxy phosphonic acid diester of formula
10 $\text{CH}(\text{OH})(\text{R}^5)\text{PO}_3(\text{R}^6)_2$, (R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, R^6 is alkyl of 1-6 carbon atoms) to afford the phosphonic acid diesters of formula (Iq: A is H or OH; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or $\text{OCH}_2\text{CO}_2\text{R}^6$, but Y and Z are not concurrently $\text{OCH}_2\text{CO}_2\text{R}^6$; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6
15 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is $\text{PO}_3(\text{R}^6)_2$; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, R^6 is alkyl of 1-6 carbon atoms; E is S, O) under the conditions of the Mitsunobu Reactions (for a review see Oyo Mitsunobu *Synthesis* 1981, 1-27). The other co-reagents necessary to effect the
20 Mitsunobu Reaction include one or more molar equivalents of a alkyl of 1-6 carbon atoms azodicarboxylate diester such as diethyl azodicarboxylate or diisopropyl azodicarboxylate and one or more molar equivalents of triarylphosphine such as triphenylphosphine in a suitable solvent such as diethyl ether, THF, benzene or toluene at temperatures ranging from -20°C to 120°C . The 2-hydroxy phosphonic acid
25 diester of formula $\text{CH}(\text{OH})(\text{R}^5)\text{PO}_3\text{R}^6$ (R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, R^6 is alkyl of 1-6 carbon atoms) can be prepared by reacting a dialkylphosphonate of formula $\text{HP}(\text{O})(\text{OR}^6)_2$ (R^6 is alkyl of 1-6 carbon atoms) with an aldehyde of formula R^5CHO (R^5 is alkyl of 1-6 carbon atoms, aryl, aralkyl) under standard conditions.

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The phosphonic acid diesters of formula (Iq): A is H or OH; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or $\text{OCH}_2\text{CO}_2\text{R}^6$, but Y and Z are not concurrently $\text{OCH}_2\text{CO}_2\text{R}^6$; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is $\text{PO}_3(\text{R}^6)_2$; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, R^6 is H, alkyl of 1-6 carbon atoms; E is S, O) can be transformed into their phosphonic acid analogs using standard conditions to afford the phosphonic acids of formula (Iq): A is H or OH; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H or $\text{OCH}_2\text{CO}_2\text{R}^6$, but Y and Z are not concurrently $\text{OCH}_2\text{CO}_2\text{R}^6$; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is PO_3H_2 ; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, R^6 is alkyl of 1-6 carbon atoms; E is S, O). The conditions that may also be employed in which the above mentioned phosphonic acid diester of formula (Iq) is reacted with two or more molar equivalents of a mineral acid such as HCl or sulfuric acid in water with or without a co-solvent such as THF at temperatures ranging from 40 to 100°C. Still alternatively, many other conditions may be employed to effect the above mentioned diester to acid transformation leading to (Iq). These include reacting the phosphonic acid diester of formula (Iq) with two or more molar equivalents of boron tribromide or boron trichloride in dichloromethane at -78°C to room temperature; two or more molar equivalents hydrobromic acid in acetic acid at 0°C to 50°C; two or more molar equivalents trimethylsilylbromide or trimethylsilyliodide in dichloromethane, carbon tetrachloride or acetonitrile at -78°C to 50°C; two or more molar equivalents lithium iodide in pyridine or quinoline at temperatures from 60° to 250°C.

The esters of formula (Iq): A is H or OH; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy

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of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CO_2R^6 ; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $\text{CH}_2(3\text{-1H-indolyl})$, $\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2(3\text{-pyridyl})$, R^6 is alkyl of 1-6 carbon atoms; E is S, O) can be transformed into their primary carboxylic acid amide analogs of formula (Iq: A is H or OH; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CONH_2 ; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $\text{CH}_2(3\text{-1H-indolyl})$, , $\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2(3\text{-pyridyl})$; E is S, O) by reacting the ester starting material with ammonia gas dissolved in a lower alcohol solvent such as methanol or ethanol at temperatures ranging from 0°C to 100°C .

Alternatively, the carboxylic acids of formula (Iq: A is H or OH; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CO_2H ; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $\text{CH}_2(3\text{-1H-indolyl})$, $\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2(3\text{-pyridyl})$; E is S, O) can be transformed into their carboxylic acid amide analogs of formula (Iq: A is H or OH; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CONH_2 , CONHOH , $\text{CONH}(\text{CH}_2)_2\text{CN}$; R^5 is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $\text{CH}_2(3\text{-1H-indolyl})$, $\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $\text{CH}_2(3\text{-pyridyl})$; E is S, O). This

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transformation can be accomplished using standard methods to effect carboxylic acid to carboxylic acid amide transformations. These methods include converting the acid to an activated acid and reacting with one or more molar equivalents of the desired amine. Amines in this category include ammonia in the form of ammonium
5 hydroxide, hydroxyl amine and 2-aminopropionitrile. Methods to activate the carboxylic acid include reacting said acid with one or more molar equivalents of oxalyl chloride or thionyl chloride to afford the carboxylic acid chloride in a suitable solvent such as dichloromethane, chloroform or diethyl ether. This reaction is often catalyzed by adding small amounts (0.01 to 0.1 molar equivalents) of
10 dimethylformamide. Other methods to activate the carboxylic acid include reacting said acid with one or more molar equivalents dicyclohexylcarbodiimide with or without one or more molar equivalents of hydroxybenzotriazole in a suitable solvent such as dichloromethane or dimethylformamide at temperatures ranging from 0°C to 60°C.

15 The phenols of formula (Ip: A is H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl; E is S, O) can be alkylated with
20 one or more molar equivalents of a haloacetonitrile of formula (X^2CH_2CN where X^2 is Cl, Br or I) and with one or more molar equivalents of an alkali metal carbonate such as potassium carbonate in a polar aprotic solvent such as DMF to afford the nitriles of formula (Iq: A is H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon
25 atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CN; R^5 is H; E is S, O).

Alternatively, the carboxylic acid amide analogs of formula (Iq: A is H or OH; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon
30 atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN,

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perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CONH₂; R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH₂(1H-imidazol-4-yl), CH₂(3-1H-indolyl), CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl), CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), CH₂(3-pyridyl) ; E is S, O) can be converted to their nitrile analogs of formula (Iq: A is H or OH; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CN; R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH₂(1H-imidazol-4-yl), CH₂(3-1H-indolyl), CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl), CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), CH₂(3-pyridyl) ; E is S, O) by using reagents that dehydrate the primary carboxamide function to the nitrile function. One set of conditions to effect this transformation include reacting the said primary carboxylic acid amide with one or more molar equivalents of trifluoroacetic anhydride and two or more molar equivalents of pyridine in a suitable solvent such as dioxane at temperatures ranging from 60°C to 120°C.

The nitrile analogs of formula (Iq: A is H or OH; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CN; R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH₂(1H-imidazol-4-yl), CH₂(3-1H-indolyl), CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl), CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), CH₂(3-pyridyl) ; E is S, O) can be converted to the tetrazoles of formula (Iq: A is H or OH; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethyl-

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amino-ethylsulfanyl; W is 5-tetrazole; R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH₂(1H-imidazol-4-yl), CH₂(3-1H-indolyl), CH₂CH₂(1,3-dioxo-1,3-dihydro-isindol-2-yl), CH₂CH₂(1-oxo-1,3-dihydro-isindol-2-yl), CH₂(3-pyridyl) ; E is S, O) by reacting the nitrile function with one or more molar equivalents of trimethylaluminum and one or more molar equivalents of trimethylsilyl azide in a suitable solvent such as benzene or toluene at temperatures ranging from 60°C to 120°C. Alternatively, the nitrile function can be reacted with one or more molar equivalents of ammonium azide in a suitable solvent such as dimethylformamide at temperatures ranging from 60°C to 160°C.

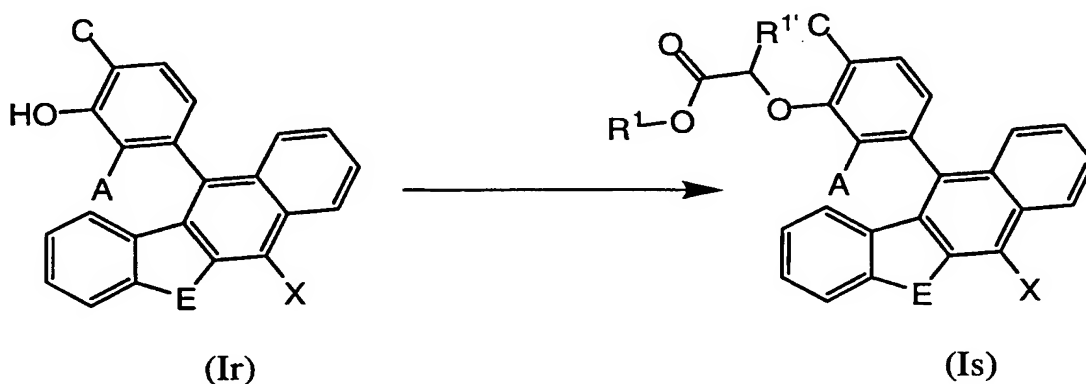
10 The esters of formula (Iq: A is H; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CO₂R⁶; R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl, aryl; R⁶ is alkyl of 1-6 carbon atoms; E is S, O) can be transformed into their primary alcohol analogs of formula (Iq: A is H; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CH₂OH; R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl, aryl; R⁶ is alkyl of 1-6 carbon atoms; E is S, O) by reacting said ester with one or more molar equivalents of lithium aluminum hydride and one or more molar equivalents of aluminum chloride in a suitable solvent such as THF at temperatures ranging from -78 to room temperature.

25 The primary alcohol analogs of formula (Iq: A is H; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CH₂OH; R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl, aryl; R⁶ is alkyl of 1-6 carbon atoms; E is S, O) can be

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converted to the primary bromides of formula (Iq): A is H; B, D is H, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms; Y, Z is H; X is H, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; W is CH₂Br; R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl, aryl; R⁶ is alkyl of 1-6 carbon atoms; E is S, O) by reacting the said primary alcohol with one or more molar equivalents of lithium bromide with one or more molar equivalents of a alkyl of 1-6 carbon atoms azocarboxylate diester such as diethyl azodicarboxylate or diisopropyl azodicarboxylate and one or more molar equivalents of triarylphosphine such as triphenylphosphine in a suitable solvent such as diethyl ether, THF, benzene or toluene at temperatures ranging from -20°C to 120°C.

Scheme 10

Further derivatives of the compounds of formula (I) in Scheme 10 can be prepared by the following methods. The phenols of formula (Ir: A is H or halogen; C is halogen or methoxy; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be reacted with a 2-hydroxy carboxylic acid ester of formula CH(OH)(R^{1a})CO₂R¹ (R¹, R^{1a} is alkyl of 1-6 carbon atoms, aralkyl, aryl) to afford the esters of formula (Is: A is H or halogen; C is halogen or methoxy; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon

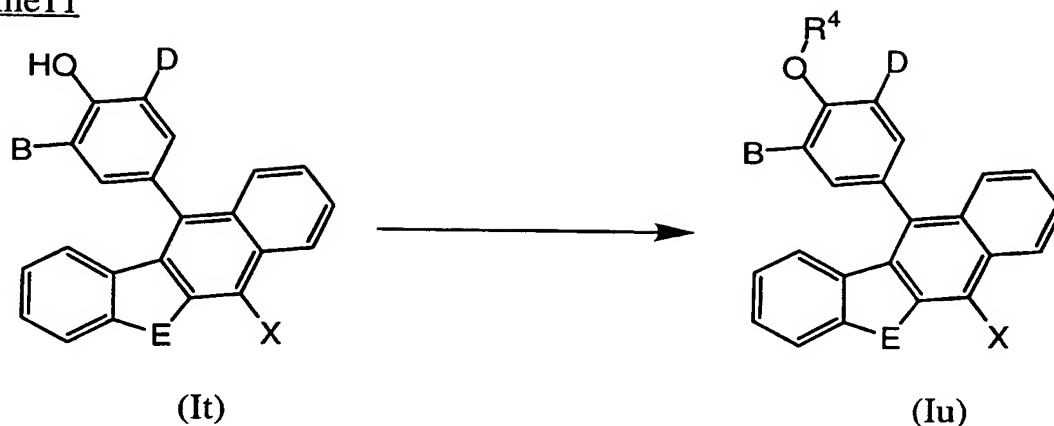
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atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridyl-sulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R¹ is alkyl of 1-6 carbon atoms, aralkyl, aryl; R^{1a} is H or alkyl of 1-6 carbon atoms, aralkyl, aryl; E is S, O) under the conditions of the Mitsunobu Reactions (for a review see Oyo Mitsunobu *Synthesis*
5 1981, 1-27). The other co-reagents necessary to effect the Mitsunobu Reaction include one or more molar equivalents of a alkyl of 1-6 carbon atoms azodicarboxylate diester such as diethyl azodicarboxylate or diisopropyl azodicarboxylate and one or more molar equivalents of triarylphosphine such as triphenylphosphine in a suitable solvent such as diethyl ether, THF, benzene or
10 toluene at temperatures ranging from -20°C to 120°C at temperatures ranging from -20°C to 120°C.

The 2-hydroxy carboxylic acid ester of formula CH(OH)(R^{1a})CO₂R¹ (R¹, R^{1a} s alkyl of 1-6 carbon atoms, aralkyl, aryl) are commercially available or can be prepared from commercially available carboxylic acid precursors under standard
15 esterification conditions.

The esters of formula (Is: A is H or halogen; C is halogen or methoxy; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl R¹ is alkyl of 1-6 carbon atoms, aralkyl, aryl; R^{1a} is H or alkyl of 1-6 carbon atoms, aralkyl, aryl; E is S, O) can be
20 transformed into their carboxylic acid analogs using standard conditions to afford the carboxylic acids of formula (Is: A is H or halogen; C is halogen or methoxy; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R¹ H; R^{1a} is H or alkyl of 1-6
25 carbon atoms, aralkyl, aryl; E is S, O). The conditions to effect these transformations include aqueous base in which one or more molar equivalents of alkali metal hydroxide such as sodium hydroxide is used in water with a co-solvent such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol
30 at temperatures ranging from 0°C to 40°C.

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Scheme 11

Further derivatives of the compounds of formula (I) in Scheme 11 can be prepared by the following methods. The phenols of formula (It: B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is

5 halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be reacted with one or more molar equivalents of lithium (bis)trimethylsilylamide at temperatures ranging from -78°C to room temperature and the lithium salt can be further reacted

10 with one or more molar equivalents of 5-bromothiazolidine-2, 4-dione (prepared according to the method of Zask, et al., *J. Med Chem*, **1990**, 33, 1418-1423) using a suitable solvent such as THF under an inert atmosphere at temperatures ranging from -78°C to room temperature to provide the compounds of formula (Iu: R⁴ is (R, S)-5-thiazolidine-2,4-dione; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl,

15 aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O).

Alternatively, the phenols of formula (It: B, D is H, halogen, CN, alkyl of 1-6

20 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridyl-

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sulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be reacted with one or more molar equivalents of tetrazole and di-tert-butyl N,N-diethylphosphoramidate in THF at room temperature followed by addition of one or more molar equivalents of meta-chlorobenzoic acid at -40°C according to the procedure of J. W. Perich and R. B. Johns, *Synthesis*, **1988**, 142-144) to afford the phosphate diesters of formula (Iu: R⁴ is P(O)(OtBu)₂; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O). These phosphate diesters are then treated with one or more molar equivalents hydrochloric acid in a suitable solvent such as dioxane to provide the phosphonic acids of formula (Iu: R⁴ is P(O)(OH)₂; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O).

The phenols of formula (It: B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be transformed to the carboxylic acids of formula (Iu: R⁴ is C(CH₃)₂CO₂H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) by treatment of the phenols with two or more molar equivalents of solid sodium hydroxide followed by one or more molar equivalents of 1,1,1-trichloro-2-methyl-2-propanol tetrahydrate in the presence of a large excess of acetone which also serves as solvent.

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The phenols of formula (It: B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be transformed to the carboxylic acids of formula (Iu: R⁴ is CH₂CH₂CO₂H; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) by treatment with one or more molar equivalents of β-propiolactone and treatment with one or more molar equivalents of potassium tert-butoxide in a suitable solvent such as THF.

The phenols of formula (It: B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; E is S, O) can be reacted with a 3-hydroxy carboxylic acid ester of formula CH(OH)(R⁷)CH₂CO₂R⁶ (R⁷ is H or alkyl of 1-6 carbon atoms; R⁶ is alkyl of 1-6 carbon atoms) to afford the esters of formula (Iu: R⁴ is (R)-CH(R⁷)CH₂CO₂R⁶; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R⁷ is H or alkyl of 1-6 carbon atoms; R⁶ is alkyl of 1-6 carbon atoms; E is S, O) under the conditions of the Mitsunobu Reactions (for a review see Oyo Mitsunobu *Synthesis* 1981, 1-27). The other co-reagents necessary to effect the Mitsunobu Reaction include one or more molar equivalents of a alkyl of 1-6 carbon atoms azodicarboxylate diester such as diethyl azodicarboxylate or diisopropyl azodicarboxylate and one or more molar equivalents of triarylphosphine such as triphenylphosphine in a suitable solvent such as diethyl ether, THF, benzene or

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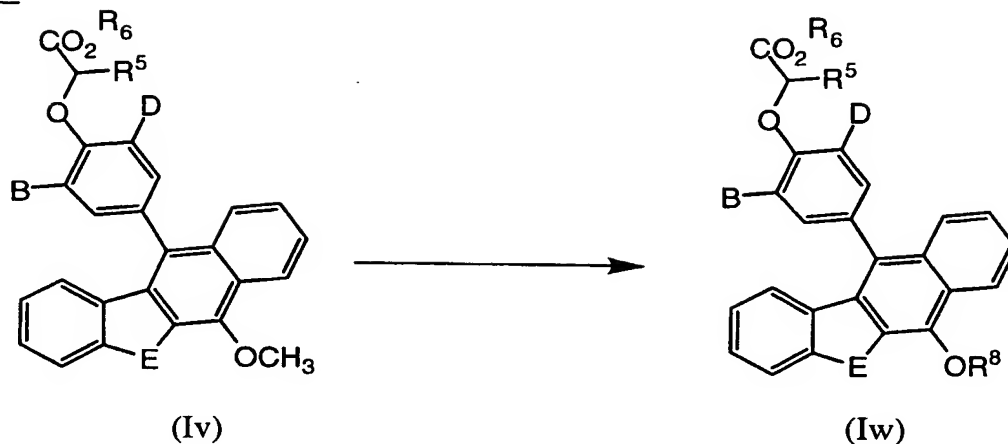
toluene at temperatures ranging from -20°C to 120°C at temperatures ranging from -20°C to 120°C.

The 3-hydroxy carboxylic acid ester of formula $\text{CH}(\text{OH})(\text{R}^7)\text{CH}_2\text{CO}_2\text{R}^6$ (R^7 is H or alkyl of 1-6 carbon atoms; R^6 is alkyl of 1-6 carbon atoms) are commercially available or can be prepared from commercially available carboxylic acid precursors under standard esterification conditions.

The esters of formula (Iu: R^4 is $(\text{R})\text{-CH}(\text{R}^7)\text{CH}_2\text{CO}_2\text{R}^6$; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R^7 is H or alkyl of 1-6 carbon atoms; R^6 is alkyl of 1-6 carbon atoms; E is S, O) can be transformed to the acids of formula (Iu: R^4 is $(\text{R})\text{-CH}(\text{R}^7)\text{CH}_2\text{CO}_2\text{H}$; B, D is H, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl, alkoxy of 1-6 carbon atoms, nitro; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, nitro, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylamino-ethylsulfanyl; R^7 is H or alkyl of 1-6 carbon atoms; E is S, O) by several standard conditions which include reacting the ester of formula (Iu) with two or more molar equivalents of a mineral acid such as HCl or sulfuric acid in one or more solvents or a combination of two or more solvents such as water, THF or dioxane at temperatures ranging from 40 to 120°C. Still alternatively, many other conditions may be employed to effect the above mentioned ester to acid transformation leading to (Iu). These include reacting the esters of formula (Iu) with two or more molar equivalents of boron tribromide or boron trichloride in dichloromethane at -78°C to room temperature; two or more molar equivalents hydrobromic acid in acetic acid at 0°C to 50°C; two or more molar equivalents trimethylsilylbromide or trimethylsilyliodide in dichloromethane, carbon tetrachloride or acetonitrile at -78°C to 50°C; two or more molar equivalents lithium iodide in pyridine or quinoline at temperatures from 60° to 250°C.

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Scheme 12



Further derivatives of the compounds of formula (I) in Scheme 12 can be prepared by the following methods. The esters of formula (Iv: B, D is H, halogen, alkyl of 1-6 carbon atoms; R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is alkyl of 1-6 carbon atoms; E is S, O) can be reacted with one or more molar equivalents of boron tribromide in a halocarbon solvent such as dichloromethane at temperatures ranging from -78 to room temperature to provide the phenols of formula (Iw: B, D is H, halogen, alkyl of 1-6 carbon atoms; R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is alkyl of 1-6 carbon atoms; R⁸ is H; E is S, O).

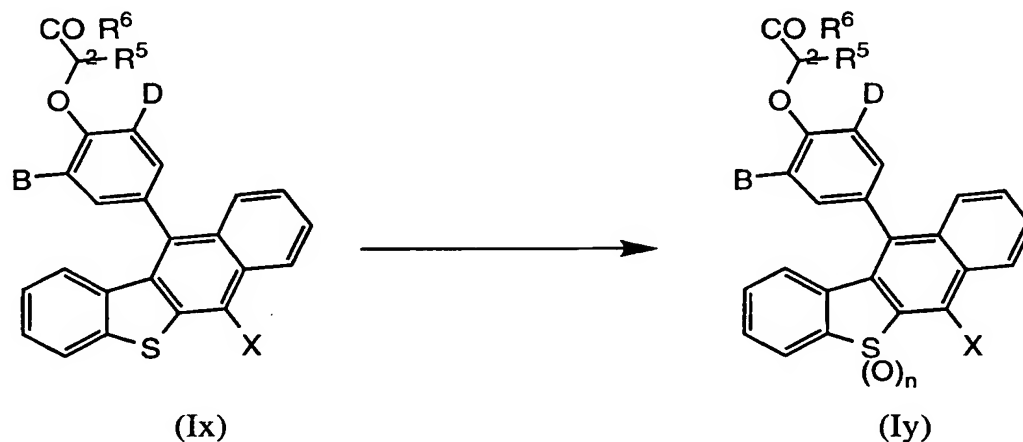
The phenols of formula (Iw: B, D is H, halogen, alkyl of 1-6 carbon atoms; R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is alkyl of 1-6 carbon atoms; R⁸ is H; E is S, O) can be alkylated with one or more molar equivalents of an alkylating agent of formula R⁸X (R⁸ is alkyl of 1-6 carbon atoms, lower aralkyl and CH₂CO₂CH₃; X is halogen; E is S, O) and with one or more molar equivalents of an alkali metal carbonate such as potassium carbonate in a polar aprotic solvent such as DMF to afford the alkylated phenol of formula (Iw: B, D is H, halogen, alkyl of 1-6 carbon atoms; R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is alkyl of 1-6 carbon atoms; R⁸ is alkyl of 1-6 carbon atoms, lower aralkyl, CH₂CO₂CH₃; E is S, O).

The esters of formula (Iw: B, D is H, halogen, alkyl of 1-6 carbon atoms; R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is alkyl of 1-6 carbon atoms; R⁸ is alkyl of 1-6 carbon atoms, lower aralkyl, CH₂CO₂CH₃; E is S, O) can be transformed into their carboxylic acid analogs using standard conditions to afford the carboxylic

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acids of formula (Iw: B, D is H, halogen, alkyl of 1-6 carbon atoms; R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is H; R⁸ is alkyl of 1-6 carbon atoms, lower aralkyl, CH₂CO₂H; E is S, O). The conditions to effect these transformations include

5 as sodium hydroxide is used in water with a co-solvent such as THF, dioxane or a lower alcohol such as methanol or mixtures of THF and a lower alcohol at temperatures ranging from 0°C to 40°C.

Scheme 13

Further derivatives of the compounds of formula (I) in Scheme 13 can be

10 prepared by the following methods. The compounds of formula (Ix: B, D is H, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is H, alkyl of 1-6 carbon atoms) can be transformed into their sulfoxide derivatives of formula (Iy:

15 n is 1; B, D is H, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is H, alkyl of 1-6 carbon atoms) using one molar equivalent of an oxidizing agent such as m-chloroperbenzoic acid in dichloromethane at temperatures ranging from

20 -20°C to 40°C or peracetic acid in acetic acid and water at temperatures ranging from room temperature to 100°C.

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The compounds of formula (Ix: B, D is H, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is H, alkyl of 1-6 carbon atoms) can be transformed into their sulfone derivatives of formula (Iy: n is 2; B, D is H, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms; X is halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aralkoxy, R⁵ is H, alkyl of 1-6 carbon atoms, aryl or aralkyl; R⁶ is H, alkyl of 1-6 carbon atoms) using two or more molar equivalents of an oxidizing agent such as m-chloroperbenzoic acid in dichloromethane at temperatures ranging from -20°C to 60°C or peracetic acid in acetic acid and water at temperatures ranging from room temperature to 100°C.

The compounds of this invention are useful in treating metabolic disorders related to insulin resistance or hyperglycemia, typically associated with obesity or glucose intolerance. The compounds of this invention are therefore, particularly useful in the treatment or inhibition of type II diabetes. The compounds of this invention are also useful in modulating glucose levels in disorders such as type I diabetes.

The ability of compounds of this invention to treat or inhibit disorders related to insulin resistance or hyperglycemia was established with representative compounds of this invention in the following two standard pharmacological test procedures which measure the inhibition of PTPase.

25

Inhibition of tri-phosphorylated insulin receptor dodecaphosphopeptide dephosphorylation by rat hepatic protein-tyrosine phosphatases (PTPases)

This standard pharmacological test procedure assess the inhibition of rat hepatic microsomal PTPase activity using, as substrate, the phosphotyrosyl dodecapeptide corresponding to the 1142-1153 insulin receptor kinase domain,

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phosphorylated on the 1146, 1150 and 1151 tyrosine residues. The procedure used and results obtained are briefly outlined below.

- Preparation of Microsomal Fraction: Rats (Male Sprague-Dawley rats (Charles River, Kingston, NY) weighing 100-150 g, maintained on standard rodent chow (Purina)) are sacrificed by asphyxiation with CO₂ and bilateral thoracotomy. The liver is removed and washed in cold 0.85% (w/v) saline and weighed. The tissue is homogenized on ice in 10 volumes of Buffer A and the microsomes are isolated essentially as described by Meyerovitch J, Rothenberg P, Shechter Y, Bonner-Weir S, Kahn CR. Vanadate normalizes hyperglycemia in two mouse models of non-insulin-dependent diabetes mellitus. *J Clin Invest* **1991**; 87:1286-1294 and Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD, editors. *Molecular biology of the cell*. New York: Garland Publishing, Inc., 1989 with minor modifications. The liver homogenate is filtered through silk to remove any remaining tissue debris and then is centrifuged at 10,000xg for 20 minutes at 40C. The supernatant is decanted and centrifuged at 100,000xg for 60 minutes at 40C. The pellet, microsomes and small vesicles, is resuspended and lightly homogenized in : 20 mM TRIS-HCl (pH 7.4), 50 mM 2-mercaptoethanol, 250 mM sucrose, 2 mM EDTA, 10 mM EGTA, 2 mM AEBSF, 0.1 mM TLCK, 0.1 mM TPCK, 0.5 mM benzamidine, 25 ug/ml leupeptin, 5 ug/ml pepstatin A, 5 ug/ml;H5B antipain, 5 ug/ml chymostatin, 10 ug/ml aprotinin (Buffer A), to a final concentration of approximately 850 ug protein/ml. Protein concentration is determined by the Pierce Coomassie Plus Protein Assay using crystalline bovine serum albumin as a standard (Pierce Chemical Co., Rockford, IL).
- Measurement of PTPase activity: The malachite green-ammonium molybdate method, as described by Lanzetta PA, Alvarez LJ, Reinach PS, Candia OA was used. An improved assay for nanomolar amounts of inorganic phosphate. *Anal. Biochem.* **1979**;100:95-97, and adapted for the platereader, is used for the nanomolar detection of liberated phosphate by rat hepatic microsomal PTPases. The test procedure uses, as substrate, a dodecaphosphopeptide custom synthesized by AnaSpec, Inc. (San Jose, CA). The peptide, TRDIYETDYRK, corresponding to the 1142-1153 catalytic

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domain of the insulin receptor, is tyrosine phosphorylated on the 1146, 1150 and 1151 tyrosine residues. The microsomal fraction (83.25 ul) is preincubated for 10 min at 37deg.C with or without test compound (6.25ul) and 305.5 ul of the 81.83 mM HEPES reaction buffer, pH 7.4. Peptide substrate, 10.5 ul at a final concentration of 50 uM, is equilibrated to 37deg.C in a LABLINE Multi-Blok heater equipped with a titerplate adapter. The preincubated microsomal preparation (39.5 ul) with or without drug is added to initiate the dephosphorylation reaction, which proceeds at 37deg.C for 30 min. The reaction is terminated by the addition of 200 ul of the malachite green-ammonium molybdate-Tween 20 stopping reagent (MG/AM/Tw). The stopping reagent consists of 3 parts 0.45% malachite green hydrochloride, 1 part 4.2% ammonium molybdate tetrahydrate in 4 N HCl and 0.5% Tween 20. Sample blanks are prepared by the addition of 200 ul MG/AM/Tw to substrate and followed by 39.5 ul of the preincubated membrane with or without drug. The color is allowed to develop at room temperature for 30 min and the sample absorbances are determined at 650 nm using a platereader (Molecular Devices). Samples and blanks are prepared in quadruplicates. Screening activity of 50 uM (final) drug is assessed for inhibition of microsomal PTPases.

Calculations: PTPase activities, based on a potassium phosphate standard curve, are expressed as nmoles of phosphate released/min/mg protein. Test compound PTPase inhibition is calculated as percent of control. A four parameter non-linear logistic regression of PTPase activities using SAS release 6.08, PROC NLIN, is used for determining IC50 values of test compounds. All compounds were administered at a concentration of 50 μ M. The following results were obtained using representative compounds of this invention.

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Example	% Change from Control
7	1.03
14	-34.19
15	-43.68
18	-15.22
20	-26.86
21	-32.41
22	-16.83
23	-8.92
24	3.16
25	-38.31
26	-8.68
27	-35.78
30	1.00
32	-58.12
34	-3.40
37	-3.02
40	-1.40
41	-39.32
42	-21.28
43	-14.62
47	-3.50
58	-43.32
59	-35.46
60	-25.07
61	-54.82
62	-40.14
63	-47.53
64	-15.90
68	-26.32
70	-29.03
71	-35.74
74	-21.61
76	-18.89
79	-82.58
81	-47.69
82	-39.80
83	-57.89
84	-73.91
85	-71.67

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Example	% Change from Control
86	-69.35
87	-63.18
88	-67.03
89	-61.04
90	-79.04
91	-97.10
92	-98.16
93	-58.35
94	-95.80
95	-75.45
108	-72.94
109	-66.67
110	-12.78
111	-76.45
113	-101.01
114	-68.03
115	-55.43
116	-61.89
117	-79.06
118	-82.00
119	-75.29
120	-17.35
121	-74.70
122	-85.46
123	-87.44
124	-70.01
125	-73.96
126	-78.77
127	-37.08
128	-50.94
129	-59.03
130	-72.14
131	-66.21
132	-49.27
133	-27.89
134	-69.86
135	-59.75
136	-63.42

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Example	% Change from Control
137	-64.92
138	-69.13
139	-64.89
140	-71.19
141	-76.58
142	-104.68
143	-76.98
144	-85.24
146	-71.95
147	-66.60
148	-82.62
149	-59.82
150	-92.46
152	-95.22
155	-82.25
156	-71.12
161	-8.03
162	-60.67
163	-38.40
164	-70.32
165	-3.12
166	-26.86
167	-16.99
168	-17.85
169	-9.30
170	-18.79
171	-71.04
172	-70.95
174	0.39
175	-69.20
177	-69.35
178	-42.41
179	-66.27
180	-50.64
184	-46.44
185	-98.45
186	-74.87
187	-57.64
189	-89.32

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Example	% Change from Control
194	-79.35
195	-29.34
196	-80.08
200	-50.62
201	-75.75
203	-86.47
210	-51.55
211	-36.82
213	-54.40
215	-80.93
216	-60.67
217	-80.42
Phenylarsine oxide (reference standard)	-57.06

Inhibition of Tri-Phosphorylated Insulin Receptor Dodecaphosphopeptide

5 Dephosphorylation by hPTP1B

This standard pharmacological test procedure assess the inhibition of recombinant rat protein tyrosine phosphatase, PTP1B, activity using, as substrate, the phosphotyrosyl dodecapeptide corresponding to the 1142-1153 insulin receptor kinase domain, phosphorylated on the 1146, 1150 and 1151 tyrosine residues. The procedure used and results obtained are briefly described below.

Human recombinant PTP1B was prepared as described by Goldstein (see Goldstein et al. *Mol. Cell. Biochem.* **109**, 107, **1992**). The enzyme preparation used was in microtubes containing 500-700 µg/ml protein in 33 mM Tris-HCl, 2 mM EDTA, 10% glycerol and 10 mM 2-mercaptoethanol.

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Measurement of PTPase activity. The malachite green-ammonium molybdate method, as described (Lanzetta et al. *Anal. Biochem.* **100**, 95, 1979) and adapted for a platereader, is used for the nanomolar detection of liberated phosphate by recombinant PTP1B. The test procedure uses, as substrate, a dodecaphosphopeptide custom synthesized by AnaSpec, Inc. (San Jose, CA). the peptide, TRDIYETDYYRK, corresponding to the 1142-1153 catalytic domain of the insulin receptor, is tyrosine phosphorylated on the 1146, 1150, and 1151 tyrosine residues. The recombinant rPTP1B is diluted with buffer (pH 7.4, containing 33 mM Tris-HCl, 2 mM EDTA and 50 mM b-mercaptoethanol) to obtain an approximate activity of 1000-2000 nmoles/min/mg protein. The diluted enzyme (83.25 mL) is preincubated for 10 min at 37°C with or without test compound (6.25 mL) and 305.5 mL of the 81.83 mM HEPES reaction buffer, pH 7.4 peptide substrate, 10.5 ml at a final concentration of 50 mM, and is equilibrated to 37°C. in a LABLINE Multi-Blok heater equipped with a titerplate adapter. The preincubated recombinant enzyme preparation (39.5 ml) with or without drug is added to initiate the dephosphorylation reaction, which proceeds at 37°C for 30 min. The reaction is terminated by the addition of 200 mL of the malachite green-ammonium molybdate-Tween 20 stopping reagent (MG/AM/Tw). The stopping reagent consists of 3 parts 0.45% malachite green hydrochloride, 1 part 4.2% ammonium molybdate tetrahydrate in 4 N HCl and 0.5% Tween 20. Sample blanks are prepared by the addition of 200 mL MG/AM/Tw to substrate and followed by 39.5 ml of the preincubated recombinant enzyme with or without drug. The color is allowed to develop at room temperature for 30 min. and the sample absorbances are determined at 650 nm using a platereader (Molecular Devices). Sample and blanks are prepared in quadruplicates.

25

Calculations: PTPase activities, based on a potassium phosphate standard curve, are expressed as nmoles of phosphate released/min/mg protein. Inhibition of recombinant PTP1B by test compounds is calculated as percent of phosphatase control. A four parameter non-linear logistic regression of PTPase activities using SAS release 6.08,

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PROC NLIN, is used for determining IC₅₀ values of test compounds. The following results were obtained.

Example	IC ₅₀ (μM)
18	0.554
21	0.384
37	1.18
40	1.10
41	1.08
42	1.50
43	0.189
58	1.01
59	0.612
60	0.129
62	0.654
63	0.904
64	0.347
68	1.02
70	0.074
71	0.079
79	0.386
81	1.99
82	2.00
87	1.68
89	0.126
91	1.30
92	0.644
108	0.061
109	0.071
110	1.52
111	0.062
113	0.045
114	0.589
115	0.279
116	0.765
117	1.51
118	0.031
120	0.541
121	0.184

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Example	IC50 (μ M)
122	0.036
123	0.082
124	0.085
126	0.298
127	0.064
128	0.025
129	0.046
130	0.80
132	0.311
133	0.506
134	0.093
135	0.209
136	0.050
137	0.341
138	0.636
139	0.061
140	0.204
141	0.126
142	0.103
143	1.17
144	1.13
146	0.064
148	1.23
150	0.207
152	0.994
155	0.056
156	0.026
162	0.145
165	0.665
166	0.565
168	0.994
169	1.22
170	0.607
171	0.302
172	0.076
177	1.08
178	0.480
179	0.203
180	0.384
184	0.045

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Example	IC50 (μ M)
189	1.39
190	2.00
191	0.118
194	0.217
195	0.889
196	0.174
200	1.17
203	0.402
210	1.06
215	0.49
216	0.083
Phenylarsine oxide (reference standard)	39.7
Sodium orthovanadate (reference standard)	244.8
Ammonium molybdate tetrahydrate (reference standard)	8.7

The blood glucose lowering activity of representative compounds of this invention were demonstrated in an in vivo standard procedure using diabetic (ob/ob) mice. The procedures used and results obtained are briefly described below.

The non-insulin dependent diabetic (NIDDM) syndrome can be typically characterizes by obesity, hyperglycemia, abnormal insulin secretion, hyperinsulinemia and insulin resistance. The genetically obese-hyperglycemic ob/ob mouse exhibits many of these metabolic abnormalities and is thought to be a useful model to search for hypoglycemic agents to treat NIDDM [Coleman, D.: Diabetologia 14: 141-148, 1978].

In each test procedure, mice [Male or female ob/ob (C57 Bl/6J) and their lean littermates (ob/+ or +/+, Jackson Laboratories) ages 2 to 5 months (10 to 65 g)] of a similar age were randomized according to body weight into 4 groups of 10 mice. The mice were housed 5 per cage and are maintained on normal rodent chow with water ad libitum. Mice received test compound daily by gavage (suspended in 0.5 ml of 0.5% methyl cellulose); dissolved in the drinking water; or admixed in the diet. The dose of compounds given ranges from 2.5 to 200 mg/kg body weight/day. The dose is calculated based on the fed weekly body weight and is expressed as active moiety.

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The positive control, ciglitazone (5-(4-(1-methylcyclohexylmethoxy)benzyl)-2,4-dione, see Chang, A., Wyse, B., Gilchrist, B., Peterson, T. and Diani, A. Diabetes 32: 830-838, 1983.) was given at a dose of 100 mg/kg/day, which produces a significant lowering in plasma glucose. Control mice received vehicle only.

5 On the morning of Day 4, 7 or 14 two drops of blood (approximately 50 ul) were collected into sodium fluoride containing tubes either from the tail vein or after decapitation. For those studies in which the compound was administered daily by gavage the blood samples were collected two hours after compound administration. The plasma was isolated by centrifugation and the concentration of glucose is
10 measured enzymatically on an Abbott V.P. Analyzer.

For each mouse, the percentage change in plasma glucose on Day 4, 7 or 14 is calculated relative to the mean plasma glucose of the vehicle treated mice. Analysis of variance followed by Dunett's Comparison Test (one-tailed) are used to estimate the significant difference between the plasma glucose values from the control group
15 and the individual compound treated groups (CMS SAS Release 5.18).

The results shown in the table below shows that the compounds of this invention are antihyperglycemic agents as they lower blood glucose levels in diabetic mice.

20

Example	Dose (mg/Kg)	% Change Glucose from Vehicle	% Change Insulin from Vehicle
70	25	-28.55	45.68 (a)
79	100	-22.6	-60.9
79	100	-22.60	-60.85
87	100	-15.77 (a)	-87.97
89	10	-24.9	b
108	100	-45.83	-72.56
108	75	-49.74	-89.61
108	50	-34.79	-84.77
108	25	-25.66	-71.03
108	10	-26.09	-30.33 (a)
109	25	-26.31	-71.64
111	100	-39.36	-17.85 (a)
113	25	-0.50 (a)	-55.84
115	100	-33.9	52.00
117	100	-14.5 (a)	-83.8

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Example	Dose (mg/Kg)	% Change Glucose from Vehicle	% Change Insulin from Vehicle
121	100	-54.57	-87.76
121	10	1.37 (a)	-41.81
122	100	-28.13	-37.40
123	75	-23.96	-40.94
125	95	-27.58	-89.68
126	25	-28.55	-62.39
127	25	-18.75 (a)	-76.54
128	25	3.10 (a)	-38.83
129	25	-14.86 (a)	-54.58
131	25	-3.63 (a)	-67.55
135	25	-15.83 (a)	-57.43
136	25	-23.63	-52.05
138	25	-13.84 (a)	-91.90
139	25	-18.5 (a)	-22.00
146	100	-45.79	-56.19
155	25	-28.89	-63.23
172	100	5.62 (a)	-52.05
189	100	-46.8	11.00 (a)
191	25	-36.5	-64.3
191	10	-22.8	b
194	25	-32.0	b
203	100	-16.1 (a)	-91.0
215	100	-39.36	-4.66 (a)
216	25	-42.4	-85.6
216	25	-38.7	-84.0
216	10	-28.7	-69.4
216	5	-14.8 (a)	-55.9
Ciglitazone (reference standard)	100	-43	-39

a - no significant activity ($p < 0.05$) at this dose.

b - not measured

- 5 Based on the results obtained in the standard pharmacological test procedures, representative compounds of this invention have been shown to inhibit PTPase activity and lower blood glucose levels in diabetic mice, and are therefore useful in treating metabolic disorders related to insulin resistance or hyperglycemia, typically

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associated with obesity or glucose intolerance. More particularly, the compounds of this invention useful in the treatment or inhibition of type II diabetes, and in modulating glucose levels in disorders such as type I diabetes. As used herein, the term modulating means maintaining glucose levels within clinically normal ranges.

5

Effective administration of these compounds may be given at a daily dosage of from about 1 mg/kg to about 250 mg/kg, and may given in a single dose or in two or more divided doses. Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally,
10 via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, vaginally, and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present
15 compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal
20 forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations
25 may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic
30 acid, acacia gum, , xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Suppository formulations may be made
35 from traditional materials, including cocoa butter, with or without the addition of

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waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

5 It is understood that the dosage, regimen and mode of administration of these compounds will vary according to the malady and the individual being treated and will be subject to the judgment of the medical practitioner involved. It is preferred that the administration of one or more of the compounds herein begin at a low dose and be increased until the desired effects are achieved.

10

The following procedures describe the preparation of representative examples of this invention.

Example 1.

15 Benzo[b]thiophene-2-yl-(phenyl)-methanol

n-Butyl lithium (35 ml, 2.5 N in hexanes) was added dropwise to a stirred solution of thianaphthene (11.5 g, 85.6 mmol) in THF (300 mL) at -78°C under a dry N₂ atmosphere. After 1 h, benzaldehyde (9.6 mL, 94.4 mmol) was added and the cold bath was removed. After an additional 30 minutes, sat. aq. NH₄Cl was added and
20 the reaction mixture was partitioned between water and ether. The ether phase was washed with brine and concentrated. The resultant solid was triturated with pet. ether and filtered to provide the title compound as a white solid (17.7 g, 86%): NMR (CDCl₃); δ 7.78 (m, 1H, thiopheneH), 7.68 (m, 1H, thiopheneH), 7.22-7.56 (m, 7H), 7.12 (s, 1H, thiopheneH), 6.12 (d, 1H, OH), 2.51 (d, 1H, CH).

25

Example 2.

(6-Methoxy-benzo[b]thiophene-2-yl-(phenyl)-methanol

n-Butyl lithium (12.5 ml, 2.5 N in hexanes) was added dropwise to a stirred solution of 6-methoxythianaphthene (5.0 g, 30.4 mmol, S. L. Graham, et al., *J. Med.*
30 *Chem.* **1989**, 32, 2548-2554) in THF (70 mL) at -78°C under a dry N₂ atmosphere. After 1 h, benzaldehyde (3.42 mL, 33.4 mmol) was added. After an additional 45 minutes, sat. aq. NH₄Cl was added and the reaction mixture was partitioned between

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water and ether. The ether phase was washed with brine and silica gel was added to it. The solvent was removed and the adsorbate was flash chromatographed (eluent: 9:1 petroleum ether: ethyl acetate) to provide the title compound as a white solid (5.5 g, 66%): mp 79-80: NMR (CDCl₃); δ 7.55 (d, J = 9 Hz, 1H), d 7.49 (ddd, J = 7, 1, 1 Hz, 2H), 7.39 (ddd, J = 7, 7, 1 Hz, 2H), 7.26 (m, 1H), 7.01 (s, 1H), 6.94 (d, J = 8 Hz, 1H), 6.09 (d, J = 4 Hz, 1H), 3.85 (s, 3H), 2.46 (d, J = 4 Hz, 1H); MS (EI): 270 (25%, MI).

Example 3.

Benzo[b]thiophene-2-yl-(3-methoxy-phenyl)-methanol

Prepared according to the procedure of Example 1 and substituting m-anisaldehyde for bezaldehyde. White solid: mp 63-65°C; MS (+FAB): [M⁺] 270; Anal. Calc. for C₁₆H₁₄O₂S: C, 71.08, H, 5.22, N, 0.00. Found: C, 71.07, H, 5.16, N, 0.13.

Example 4.

2-Benzyl-benzo[b]thiophene

Trifluoroacetic acid (105 mL) was added dropwise over a 35 minute period to a stirred suspension of benzo[b]thiophene-2-yl-(phenyl)-methanol (17.6 g, 73.2 mmol), sodium borohydride (13.75 g, 364 mmol) and ether (1.3 L). After an additional 5 hours the reaction mixture was added to 10 % aqueous sodium hydroxide (1.3 L) and stirred for 30 minutes. The layers were separated and the ether phase was washed with brine (500 mL) and dried (MgSO₄). The ether phase was concentrated to provide the title compound as a white solid (15.2 g, 92%): NMR (CDCl₃); δ 7.73 (d, J = 6 Hz, 1H, thiopheneH), 7.65 (d, J = 7 Hz, 1H, thiopheneH), 7.20-7.38 (m, 7H), 7.00 (s, 1H, thiopheneH), 4.22 (s, 2H, CH₂).

Example 5.

2-Benzyl-6-methoxy-benzo[b]thiophene

Prepared from (6-methoxy-benzo[b]thiophene-2-yl-(phenyl)-methanol (Example 2) according to the procedure in Example 4. White solid: mp 60-61°C:

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NMR (CDCl₃); δ 7.53 (d, J = 9 Hz, 1H), d 7.35-7.22 (m, 6H), 6.93 (dd, J = 8, 2 Hz, 1H), 6.91 (d, J = 1 Hz, 1H), 4.19 (s, 2H), 3.84 (s, 3H); MS (EI): 254 (50%, MI); Anal. Calc. for C₁₆H₁₄OS: C, 75.56, H, 5.55, N, 0.00. Found: C, 75.62, H, 5.44, N, 0.02.

5

Example 6.2-(3-Methoxy-benzyl)-benzo[b]thiophene

Prepared from benzo[b]thiophen-2-yl-(3-methoxy-phenyl)-methanol (Example 3) according to the procedure in Example 4. White solid: mp 74-75.5°C: MS (+FAB): [M+] 254; Anal. Calc. for C₁₆H₁₄OS: C, 75.56, H, 5.55, N, 0.00. Found: C, 75.85,
10 H, 5.48, N, 0.01.

Example 7.(2-Benzyl-benzo[b]thiophen-3-yl)-(4-methoxy-phenyl)-methanone

Tin tetrachloride (9.0 mL, 76.91 mmol) was added dropwise over a 25 minute
15 period to a stirred solution of 2-benzyl-benzo[b]thiophene (14.87 g, 96.79 mmol), p-anisoyl chloride (11.75 g, 68.87 mmol) and carbon disulfide (75 mL) under a dry nitrogen atmosphere. After 6 hours, the reaction mixture was added to water and extracted with dichloromethane. The dichloromethane extract was washed with sat. aq. sodium bicarbonate and brine. The solvent was removed and the resultant solid
20 was triturated with pet. ether to give the title compound as a white solid (20.2 g, 85%): mp 135-137°C: NMR (CDCl₃); δ 7.85 (dm, J = 9 Hz, 2H), 7.73 (dm, 1H), 7.42 (dm, 1H), 7.18-7.30 (m, 7H), 6.93 (dm, J = 9 Hz, 2H), 4.21 (s, 2H, CH₂), 3.88 (s, 3H, CH₃); IR (KBr, cm⁻¹): 1650; MS (EI): 358 (100%, MI), 343 (15%), 327 (75%); Anal. Calc. for C₂₃H₁₈O₂S: C, 77.07, H, 5.06, N, 0.00. Found: C, 76.91, H, 5.02, N, -0.12.

25

Example 8.(2-Benzyl-6-methoxy-benzo[b]thiophen-3-yl)-(4-methoxy-phenyl)-methanone

Tin tetrachloride (2.0 mL, 17.09 mmol) was added dropwise over a 10 minute
period to a stirred, -78°C solution of 2-benzyl-6-methoxy-benzo[b]thiophene (2.71g,
30 10.65 mmol), anisoyl chloride (1.93 g, 11.29 mmol) and dichloromethane (41 mL)

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under a dry nitrogen atmosphere. After 1 hours at -78°C, the reaction mixture was slowly warmed to room temperature and stirred for 16 h period. The reaction mixture was added to water and extracted with ether. The ether phase was washed with brine and silica gel was added to it. The solvent was removed and the adsorbate was flash chromatographed (eluent: 9:1 petroleum ether: ethyl acetate) to provide the title compound as a white solid (2.42 g, 58%): mp 110-112°C: NMR (CDCl₃); δ 7.84 (d, J = 9 Hz, 2H), 7.31-7.18 (m, 7H), 7.92 (d, J = 9 Hz, 2H), 6.97 (dd, J = 9, 2 Hz, 1H), 4.17 (s, 2H), 3.88 (s, 3H), 3.883 (s, 3H); MS (FAB+): 389 (80%, M+H); Anal. Calc. for C₂₄H₂₀O₃S: C, 74.20, H, 5.19, N, 0.00. Found: C, 74.94, H, 5.10, N, 0.03.

10

Example 9.

4-Bromo-2, 6-diisopropylanisole

This is a modification of the procedure of Schuster, Ingeborg I.; Parvez, Masood; Freyer, Alan J. *J. Org. Chem.* **1988**, *53*, 5819. A solution of bromine (6.3 mL, 119 mmol) in acetic acid (40 mL) was added dropwise to a stirred, room temperature solution of 2, 6-diisopropylphenol (20 mL, 97.1 mmol of 90% tech. grade) in acetic acid (280 mL). After 6 h, water was added and the mixture was extracted with ether. The ether phase was dried and concentrated and the residue was flash chromatographed (petroleum ether: eluent) to provide 4-bromo-2, 6-diisopropylphenol (16.2 g, 65%) as a red oil. This oil was dissolved in DMF (50 mL), iodomethane (11.7 mL, 189 mmol) and potassium carbonate (26.3 g, 117 mL) were added to it. This reaction mixture was stirred for 5 h and diluted with water. This mixture was extracted with ether and the ether extracts were dried, concentrated and flash chromatographed (petroleum ether: eluent) to provide the title compound as a colorless oil (15.4 g, 90%): NMR (CDCl₃); δ 7.17 (s, 2H), 3.70 (s, 3H), 3.29 (septet, 1H), 1.20 (d, 12 H).

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Example 10.**3, 5-Diisopropyl, 4-methoxybenzoic acid**

This is a modification of the procedure of Schuster, Ingeborg I.; Parvez, Masood; Freyer, Alan J. *J. Org. Chem.* **1988**, *53*, 5819. A solution of n-butyllithium (2.5 N in hexanes, 13.0 mL, 32.5 mmol) was added dropwise over 20 min to a stirred, -78°C solution of 4-bromo-2, 6-diisopropylanisole (8.0 g, 29.5 mmol) in THF (185 mL). After 2 h at -78°C, the reaction mixture was cautiously added to finely ground dry ice. The resulting suspension was stirred for 20 min at room temperature and cautiously added to water. The water phase was acidified with 10% aqueous HCl and extracted with ether. The ether extracts were dried and concentrated. The resulting oil solidified upon standing. This solid was triturated with petroleum ether to provide the title compound as a white solid (5.38 g, 77%): NMR (CDCl₃); δ 7.87 (s, 2H), 3.76 (s, 3H), 3.35 (septet, 1H), 1.25 (d, 12 H).

15

Example 11.**(2-Benzyl-benzo[b]thiophen-3-yl)-(3,5-diisopropyl-4-methoxy-phenyl)-methanone**

A drop of DMF was added to a solution of oxalyl chloride (1.4 mL, 16.2 mmol), 3, 5-diisopropyl-4-methoxybenzoic acid (4.0 g, 14.7 mmol) in dichloromethane under a dry nitrogen atmosphere. After 4h the solvent was removed and the resulting solid was triturated with petroleum ether and dried in vacuo. To this solid was added 2-benzyl-benzo[b]thiophene (3.32 g, 13.4 mmol) and dichloromethane (75 mL). The resulting solution was stirred under a dry nitrogen atmosphere and cooled to -78°C. Tin tetrachloride (3.44 mL, 29.48 mmol) was added dropwise over a 20 minute period. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was added to water and extracted with ether. The ether extract was washed with water and brine. Silica gel was added and the solvent was removed. The adsorbate was flash chromatographed (gradient, petroleum ether to 95:5 petroleum ether : ethyl acetate). The solvent was removed and the solid was triturated with ether to give the title compound as a white solid (3.68 g, 62%): mp 124-125°C; NMR (CDCl₃); δ 7.75 (ddd, J = 8, 2, 1 Hz, 1H), 7.64 (s, 2H), 7.48 (ddd, J

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= 8, 2, 1, 1H), 7.30-7.19 (m, 7H), 4.22 (s, 2H), 3.80 (s, 3H) 3.35 (septuplet, J = 7 Hz, 2H), 1.19 (d, J = 7 Hz, 12H); MS (+FAB): 443 (100%, M+H); Anal. Calc. for C₂₉H₃₀O₂S: C, 78.69, H, 6.83, N, 0.00. Found: C, 78.57, H, 6.88, N, 0.14.

5

Example 12.**(2-Benzyl-benzo[b]thiophen-3-yl)-(3-methoxy-phenyl)-methanone**

Prepared from 2-benzyl-benzo[b]thiophene and m-anisoyl chloride according to the procedure in Example 8. White solid: MS (EI): [M+], 358.

10

Example 13.**(2-Benzyl-benzo[b]thiophen-3-yl)-(3,4-dimethoxy-phenyl)-methanone**

Prepared from 2-benzyl-benzo[b]thiophene and 3,4-dimethoxybenzoyl chloride according to the procedure in Example 8. White solid: MS (EI): [M+], 388.

15

Example 14.**4-Benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol**

A 1.0 M solution of boron tribromide in dichloromethane (130 mL, 130 mmol) was added slowly to a stirred solution of (2-benzyl-benzo[b]thiophen-3-yl)-(4-methoxy-phenyl)-methanone (14.5 g, 40.45 mmol) in dichloromethane (130 mL) at
20 -78°C under a dry nitrogen atmosphere. The solution was allowed to warm to ambient temperature and was stirred overnight. The reaction mixture was quenched with water and partitioned between water and dichloromethane. Silica gel was added to the dichloromethane phase and the solvent was removed. The adsorbate was flash chromatographed (eluent 4:1 pet. ether: ethyl acetate) to provide a white solid (9.75
25 g). This solid was recrystallized from acetic acid to provide off-white needles (8.78, 56%): mp: 112-116°C; NMR (CDCl₃); δ 8.33 (s, 1H), 7.94 (dt, J = 8 Hz, 1H), 7.77 (dm, J = 8 Hz, 1H), 7.64 (dm, J = 8 Hz, 1H), 7.52 (ddd, J = 8, 7, 1 Hz, 1H), 7.37 (m, 2H), 7.29 (d, J = 9 Hz, 2H), 7.11 (d, J = 9 Hz, 2H), 7.08 (m, 1H), 6.85 (dm, J = 8 Hz, 1H), 2.11 (s, 3H, acetic acid CH₃); MS (EI): 326 (100%, M⁺); Anal. Calc. for
30 C₂₂H₁₄OS•C₂H₄O₂: C, 74.59, H, 4.69, N, 0.00. Found: C, 74.40, H, 4.59, N, 0.15.

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Example 15.**11-(4-Hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-ol**

Boron tribromide (5 mL, 52.9 mmol) was added slowly to a stirred solution of (2-benzyl-6-methoxy-benzo[b]thiophen-3-yl)-(4-methoxy-phenyl)-methanone (2.30 g, 5.92 mmol) in dichloromethane (30 mL) at -78°C under a dry nitrogen atmosphere. The solution was allowed to warm to ambient temperature and was stirred for 4h. The reaction mixture was quenched with water and partitioned between water and ether. Silica gel was added to the ether phase and the solvent was removed. The adsorbate was flash chromatographed (eluent 7:3 pet. ether: ethyl acetate) to provide the title compound as a white solid (2.08 g, 96%): mp: 197-199°C; NMR (CDCl₃); δ 8.28 (s, 1H), 7.92 (d, J = 8 Hz, 1H), 7.59 (dm, J = 8 Hz, 1H), 7.50 (ddd, J = 8, 7, 1 Hz, 1H), 7.39-7.25 (m, 5H), 7.21 (d, J = 2 Hz, 1H), 7.11 (d, J = 9 Hz, 2H), 6.69 (d, J = 9 Hz, 1H), 6.57 (dd, J = 9, 2 Hz, 1H), 5.03 (s, 1H), 4.94 (s, 1H); MS (FAB+): 343 (15%, M+H); Anal. Calc. for C₂₂H₁₄O₂S: C, 77.17, H, 4.12, N, 0.00. Found: C, 76.74, H, 4.04, N, 0.02.

Example 16.**4-(6-Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenol**

Neat boron tribromide (4.3 mL, 45.2 mmol) was added dropwise to a stirred suspension of (2-benzyl-benzo[b]thiophen-3-yl)-(3,5-diisopropyl-4-methoxy-phenyl)-methanone (3.57 g, 8.07 mmol) in dichloromethane (30 mL) at -78°C under a dry nitrogen atmosphere. The solution was allowed to warm to ambient temperature and was stirred for 1.5 h. The reaction mixture was cooled to 0°C and carefully quenched with water. The reaction mixture was partitioned between water and ether. The ether phase was washed with water and brine. Silica gel was added to the ether phase and the solvent was removed. The adsorbate was flash chromatographed (gradient: 99:1 to 97:1 petroleum ether : ethyl acetate) to provide the title compound as a white solid (1.46 g, 44%): NMR (CDCl₃); δ 8.33 (s, 1H), 7.95 (ddd, J = 8, 1, 1 Hz, 1H), 7.77 (ddd, J = 8, 1, 1 Hz, 1H), 7.73 (ddd, J = 8, 1, 1 Hz, 1H), 7.53 (ddd, J = 8, 8, 1 Hz, 1H), 7.40 (ddd, J = 8, 8, 1 Hz, 1H), 7.34 (ddd, J = 8, 8, 1 Hz, 1H), 7.10 (s, 2H), 7.04 (ddd, J = 8, 8, 1

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Hz, 1H), 6.75 (ddd, J = 8, 1, 1 Hz, 1H), 5.01 (s, 1H), 3.31 (septuplet, J = 7 Hz, 2H), 1.29 (s, J = 7 Hz, 6H), 1.27 (s, J = 7 Hz, 6H); MS (+FAB): 411 (100%, M+H); Anal. Calc. for C₂₈H₂₆OS: C, 81.91, H, 6.38, N, 0.00. Found: C, 81.10, H, 6.54, N, 0.40.

5

Example 17.**3-Benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

Prepared from (2-benzyl-benzo[b]thiophen-3-yl)-(3-methoxy-phenyl)-methanone (Example 12) according to the procedure for Example 15. White solid: mp 92-94°C; MS (EI): [M+], 326; Anal. Calc. for C₂₂H₁₄OS: C, 80.95, H, 4.32, N, 0.00.

10 Found: C, 80.01, H, 4.18, N, 0.04.

Example 18.**4-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol**

Prepared from (2-benzyl-benzo[b]thiophen-3-yl)-(3,4-dimethoxy-phenyl)-methanone (Example 13) according to the procedure for Example 15. White solid: mp 188-189°C; MS (EI): [M+], 342; Anal. Calc. for C₂₂H₁₄O₂S: C, 77.17, H, 4.12, N, 0.00. Found: C, 76.47, H, 3.85, N, 0.00.

15

Example 19.20 **8-Methoxy-11-(4-methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene**

To a cold (-78°C) solution of 2-(3-methoxybenzyl)-benzo[b]thiophene (2.10 g, 8.26 mmol) and p-anisoyl chloride (1.48 g, 8.67 mmol) in anhydrous methylene chloride (31 mL) was added tin IV chloride (2.90 mL, 24.8 mmol, 3 eq) dropwise over a period of 24 minutes. After stirring overnight in the warming dry ice bath and at ambient temperature for 7 hours the reaction mixture was poured onto water (175 mL) and the organics were extracted with diethyl ether (2x300 mL). The extracts were combined, and washed with brine. Silica gel was added and the solvent was removed. The adsorbate was flash chromatographed (97/3 petroleum ether/ethyl acetate) to give the title compound as a white solid (1.92 g, 63%); mp 158-159°C; MS

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(+FAB): [M+] 370; Anal. Calc. for C₂₄H₁₈O₂S: C, 77.81, H, 4.90, N, 0.00. Found: C, 78.00, H, 4.76, N, 0.03.

Example 20.

5 11-(4-Hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-8-ol

To a cold (-75°C) solution of 8-methoxy-11-(4-methoxy-phenyl)-benzo[b]-naphtho[2,3-d]thiophene (1.92 g, 5.18 mmol) in anhydrous methylene chloride was added a solution of boron tribromide (1 M in methylene chloride, 6.74 mL, 6.74 mmol, 1.3 eq) dropwise over a period of 18 minutes. After stirring in the cold for 3.5
10 hours and at ambient temperature for approximately 19 hours the reaction mixture was quenched with water (100 mL), diluted with methylene chloride (50 mL) and the organics were extracted with diethyl ether (1x100 mL, 1x75 mL). The extracts were combined, washed with brine, and combined with silica gel. The solvents were removed and the adsorbate was flash chromatographed (74/26 petroleum ether/ethyl
15 acetate) and dried at 92°C overnight to the title compound as an off-white solid (1.07 g, 91%): mp 233-235°C; NMR (DMSO-d₆): δ 9.91 (broad s, 1H), 9.77 (broad s, 1H), 8.30 (s, 1H), 7.88 (d, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.35 (ddd, J = 8, 8, 1 Hz, 1H), 7.23 (d, J = 2 Hz, 1H), 7.15 (d, J = 8 Hz, 2H), 7.09 (ddd, J = 8, 8, 1 Hz, 1H), 7.06 - 7.00 (multiplet containing a doublet at 7.05, J = 8 Hz, 3 H), 6.71 (d, J = 8 Hz, 1H);
20 MS (+FAB): [M+] 343; Anal. Calc. for C₂₂H₁₄O₂S: C, 77.17, H, 4.12, N, 0.00. Found: C, 76.43, H, 3.82, N, 0.01.

Example 21.

2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol

25 A solution of bromine (3.1 mL, 60.17 mmol) in glacial acetic acid (30 mL) was added over a five minute period to a stirred cloudy solution of 4-benzo[b]-naphtho[2,3-d]thiophen-11-yl-phenol (5.0 g, 15.32 mmol) and potassium acetate (15.0 g, 153 mmol) in acetic acid (92 mL) at ambient temperature. An exotherm was noted and yellow precipitate resulted. After 45 minutes, the reaction mixture was added to
30 water (1 L), solid sodium thiosulfate (2 g) was added and the suspension was stirred

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for five minutes. The solid was filtered and washed with water (1L), pet. ether (2 x 300 mL), 3:1 pet. ether:ether (3 x 50 mL) and pet. ether (2 x 300 mL) and dried in vacuo to provide a tan solid (7.00 g). An additional amount crystallized from the mother liquor and was added to the total (tan solid, 8.31 g, 96%). The product was

5 95% pure at this stage, however it could be further purified by recrystallization from acetic acid to provide the title compound as a white solid: mp 226.5-227°C: NMR (CDCl₃); δ 8.35 (ddd, J = 8, 1, 1 Hz, 1H), 7.84 (ddd, J = 8, 1, 1 Hz, 1H), 7.67 (ddd, J = 8, 7, 1 Hz, 1H), 7.60 (ddd, J = 8, 1, 1 Hz, 1H), 7.55 (s, 2H), 7.49 (ddd, J = 8, 7, 1 Hz, 1H), 7.45 (ddd, J = 8, 7, 1 Hz, 1H), 7.21 (ddd, J = 8, 7, 1 Hz, 1H), 6.87 (ddd, J =

10 8, 1, 1 Hz, 1H), 6.19 (s, 1H, OH); MS (-APCI): [M-H]⁻, 3 bromine isotope pattern, 559 (25%), 561 (75%) 563 (100%) 565 (45%); Anal. Calc. for C₂₂H₁₁Br₃OS: C, 46.92, H, 1.97, N, 0.00. Found: C, 46.67, H, 1.85, N, 0.03.

Example 22.

15 11-(3,5-dibromo-4-methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene

Iodomethane (0.383 mL, 6.16 mmol) was added to a stirred suspension of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (2.13 g, 4.4 mmol), potassium carbonate (0.669 g, 4.34 mmol) and DMF (15 mL) at room temperature under a dry nitrogen atmosphere. After 3h, the reaction mixture was

20 diluted with water and the resulting solid was filtered and washed with water. The solid was taken up in dichloromethane and silica gel (40 mL) was added. The solvent was removed and the adsorbate was flash chromatographed (90:10 petroleum ether : dichloromethane) to provide the title compound as a white solid (2.0 g, 91 %): mp 238.5-239.5°C: NMR (CDCl₃); δ 8.36 (ddd, J = 8, 1, 1 Hz, 1H), 7.84 (ddd, J = 8, 1, 1

25 Hz, 1H), 7.67 (ddd, J = 8, 7, 1 Hz, 1H), 7.60 (s, 2H), 7.58 (ddd, J = 8, 1, 1 Hz, 1H), 7.50 (ddd, J = 8, 7, 1 Hz, 1H), 7.45 (ddd, J = 8, 7, 1 Hz, 1H), 7.20 (ddd, J = 8, 7, 1 Hz, 1H), 6.80 (ddd, J = 8, 1, 1 Hz, 1H), 4.11 (s, 3H, CH₃); MS (EI): [M]⁺, 3 bromine isotope pattern, 574 (35%), 576 (95%) 578 (100%) 580 (45%); Anal. Calc. for C₂₃H₁₃Br₃OS: C, 47.87, H, 2.27, N, 0.00. Found: C, 47.73, H, 1.88, N, 0.03.

30

Example 23.**11-(4-Methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene**

Prepared from benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol (Example 14) according to the procedure in Example 22. White solid (0.516 g, 50%): mp: 220-
5 221°C; NMR (DMSO-d₆); δ 8.60 (s, 1H), 8.04 (d, J = 8 Hz, 1H), 7.96 (d, J = 8 Hz, 1H), 7.57 (ddd, J = 8, 7, 1 Hz, 1H), 7.50 (ddd, J = 8, 1, 1 Hz, 1H), 7.46-7.40 (m, 3H), 7.33 (d, J = 9 Hz, 2H), 7.24 (d, J = 9 Hz, 2H), 7.14 (ddd, J = 8, 7, 1 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 3.33 (s, 3H); MS (EI): 340 (100%, MI); Anal. Calc. for C₂₃H₁₆OS: C, 81.14, H, 4.74, N, 0.00. Found: C, 81.11, H, 4.57, N, 0.14.

10

Example 24.**11-(4-Methoxy-3,5-dimethyl-phenyl)-6-methyl-benzo[b]naphtho[2,3-d]thiophene**

A suspension of 6-bromo-11-(3,5-dibromo-4-methoxy-phenyl)-benzo[b]-
naphtho[2,3-d]thiophene (1.0 g, 1.733 mmol), tetramethyl tin (2.0 mL, 14.38 mmol),
15 bis(triphenylphosphine)palladium II chloride (100 mg, 8 mol%) and DMF (8 mL) was heated in a sealed pressure vessel under argon at 100°C for 17 hours (dissolution occurred after 30 min). The reaction mixture was added water and the water was extracted with ether. Silica gel was added to the ether phase and the ether was removed. The adsorbate was flash chromatographed (96:4 petroleum ether:ethyl
20 acetate) to provide the title compound as a white solid (0.63 g, 86%): mp 154-156°C: NMR (CDCl₃); δ 8.16 (ddd, J = 8, 1, 1 Hz, 1H), 7.80 (dd, J = 8, 1 Hz, 1H), 7.70 (dd, J = 8, 1 Hz, 1H), 7.57 (ddd, J = 8, 7, 1 Hz, 1H), 7.41 (ddd, J = 8, 7, 1 Hz, 1H), 7.35 (ddd, J = 8, 8, 1 Hz, 1H), 7.07 (ddd, J = 8, 7, 1 Hz, 1H), 7.04 (s, 2H), 6.79 (dd, J = 8, 1 Hz, 1H), 3.92 (s, 3H), 2.97 (s, 3H), 2.39 (s, 6H); MS (EI): 382 (100%, MI); Anal.
25 Calc. for C₂₆H₂₂OS: C, 81.64, H, 5.80, N, 0.00. Found: C, 81.30, H, 5.99, N, 0.38.

Example 25.**2,6-Dimethyl-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

A mixture of 11-(4-methoxy-3,5-dimethyl-phenyl)-6-methyl-benzo[b]-
30 naphtho[2,3-d]thiophene (0.55 g, 1.44 mmol) and pyridinium hydrochloride (1.0 g,

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8.64 mmol) was heated in a 240°C oil bath for 1.25 hour. During this time an additional amount of pyridinium hydrochloride was added (1.0 g, 8.64 mmol). The reaction mixture was cooled to room temperature and partitioned between dilute HCl and ether. Silica gel was added to the ether phase and the solvent was removed. The adsorbate was flash chromatographed (9:1 petroleum ether:ethyl acetate) to provide a light yellow solid (340 mg). This solid was recrystallized from acetic acid to provide the title compound as a light yellow solid (0.215 g, 41%): mp 147-149°C: NMR (CDCl₃); δ 8.15 (ddd, J = 8, 1, 1 Hz, 1H), 7.80 (ddd, J = 8, 1, 1 Hz, 1H), 7.71 (ddd, J = 8, 1, 1 Hz, 1H), 7.56 (ddd, J = 8, 7, 1 Hz, 1H), 7.39 (ddd, J = 8, 7, 1 Hz, 1H), 7.35 (ddd, J = 8, 8, 1 Hz, 1H), 7.09 (ddd, J = 8, 7, 1 Hz, 1H), 7.01 (s, 2H), 6.79 (ddd, J = 8, 1, 1 Hz, 1H), 2.96 (s, 3H), 2.36 (s, 6H); MS (EI): 368 (100%, MI); Anal. Calc. for C₂₅H₂₀O₅: C, 81.49, H, 5.47, N, 0.00. Found: C, 81.62, H, 5.32, N, -0.03.

Example 26.

15 4-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diiodo-phenol

Iodine (4.5 g, 17.6 mmol) was added portionwise to a stirred, 0°C solution of 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (2.3 mL, 7.05 mmol), sodium hydroxide (97%, 0.581 g, 14.1 mmol) in methanol (46 mL) over a period of one hour and the mixture was stirred at 0°C for 1 h. and at ambient temperature for 6 h. The reaction mixture was diluted with water (200 mL) and aqueous mixture was extracted with ethyl ether (2 X 200 mL). The ethyl ether extracts were washed with 5% sodium bisulfite and water, dried with brine and anhydrous MgSO₄. Silica gel (50 mL) was added. Solvent was removed and the adsorbate was flash chromatographed (eluent 8:2 petroleum ether: methylene chloride) to provide the title compound as a white solid (2.2 g, 54%): mp 213-214 °C: MS (-FAB): [M-H]⁻, 576.8; Anal. Calc. for C₂₂H₁₂I₂O₅: C, 45.70, H, 2.09, N, 0.00. Found: C, 45.82, H, 2.07, N, 0.30.

Example 27.**4-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-iodo-phenol**

Iodine (4.5 g, 17.6 mmol) was added portionwise to a stirred, 0°C solution of 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (2.3 mL, 7.05 mmol), sodium hydroxide (97%, 0.581 g, 14.1 mmol) in methanol (46 mL) over a period of one hour and the mixture was stirred at 0°C for 1 h. and at ambient temperature for 6 h. The reaction mixture was diluted with water (200 mL) and aqueous mixture was extracted with ethyl ether (2 X 200 mL). The ethyl ether extracts were washed with 5% sodium bisulfite and water, dried with brine and anhydrous MgSO₄. Silica gel (50 mL) was added. Solvent was removed and the adsorbate was flash chromatographed (eluent 8:2 petroleum ether: methylene chloride) to provide a off-white solid (0.624 g, 20%): mp 125-128 °C: MS (EI): [M+], 452; Anal. Calc. for C₂₂H₁₃IOS: C, 58.42, H, 2.90, N, 0.00. Found: C, 58.46, H, 3.00, N, 0.09.

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Example 28.**11-(4-Methoxy-3,5-diiodo-phenyl)-benzo[b]naphtho[2,3-d]thiophene**

Prepared from 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diiodo-phenol (Example 26) according to the procedure on Example 22. White solid: mp 228-230°C: MS (EI): [M+], 592; Anal. Calc. for C₂₃H₁₄I₂OS: C, 46.65, H, 2.38, N, 0.00. Found: C, 45.95, H, 2.25, N, 0.19.

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Example 29.**11-(3-Iodo-4-methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene**

Prepared from 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-iodo-phenol (Example 27) according to the procedure on Example 22. White solid: mp 274-275°C: MS (EI): [M+], 466 (100%, MI); Anal. Calc. for C₂₃H₁₅IOS: C, 59.24, H, 3.24, N, 0.00. Found: C, 58.53, H, 3.11, N, 0.11.

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Example 30.**5-Benzo[b]naphtho[2,3-d]thiophen-11-yl-2-methoxy-isophthalonitrile**

A suspension of 11-(3,5-diiodo-4-methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene (4.55 g, 7.68 mmol) and copper (I) cyanide 3.13 g, 38.4 mmol) in 1-methyl-2-pyrrolidinone (18 mL) was heated in an 150°C oil bath under a dry nitrogen atmosphere. After 1 h the solution was added to water (200 mL) and acidified with 10% aqueous HCl. The solid was filtered and flash chromatographed (silica gel: eluent: methylene chloride) to provide the title compound as a yellow solid (2.47 g, 82%); mp 214-215 °C; MS (EI): [M+], 390 (100%, MI); Anal. Calc. for C₂₅H₁₄N₂OS: C, 76.90, H, 3.61, N, 7.17. Found: C, 76.48, H, 3.46, N, 7.17.

Example 31.**5-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-methoxy-benzonitrile**

Prepared from 11-(3-iodo-4-methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene (Example 29) according to the procedure on Example 30. White solid: mp 230-232 °C; MS (EI): [M+], 365 (100%, MI); Anal. Calc. for C₂₄H₁₅NOS: C, 78.88, H, 4.41, N, 3.83. Found: C, 77.61, H, 4.23, N, 4.10.

Example 32.**5-Benzo[b]naphtho[2,3-d]thiophen-11-yl-2-hydroxy-isophthalonitrile**

Prepared from 5-benzo[b]naphtho[2,3-d]thiophen-11-yl-2-methoxy-isophthalonitrile (Example 30) according to the procedure on Example 20. White solid: mp 274-276 °C; MS (EI): [M+], 376 (80%, MI); Anal. Calc. for C₂₄H₁₂N₂OS: C, 76.58, H, 3.21, N, 7.44. Found: C, 76.20, H, 3.19, N, 7.35.

Example 33.**5-Benzo[b]naphtho[2,3-d]thiophen-11-yl-2-hydroxy-benzonitrile**

Prepared from 5-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-methoxy-benzonitrile (Example 31) according to the procedure on Example 20. White solid: mp 231-

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232 °C: MS (EI): [M+], 351 (100%, MI); Anal. Calc. for C₂₃H₁₃NOS: C, 78.61, H, 3.73, N, 3.99. Found: C, 78.27, H, 3.59, N, 3.89.

Example 34.

5 4-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol acetate ester

Acetic anhydride (0.62 mL, 6.57 mmol) was added to a 0°C, stirred solution of 4-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol (2.0 g, 6.13 mmol) in pyridine (8 mL). After 7 h the reaction mixture was added to water and the resulting solid was filtered and washed with water and dried in vacuo to provide the title compound as a
10 white solid (2.23 g, 99%): mp: 160-161°C; NMR (CDCl₃); δ 8.36 (s, 1H), 7.95 (d, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.53 (ddd, J = 8, 7, 1 Hz, 1H), 7.47-7.33 (m, 6H), 7.08 (ddd, J = 8, 7, 1 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 2.42 (s, 3H, CH₃); MS (EI): 368 (100%, MI); Anal. Calc. for C₂₄H₁₆O₂S: C, 78.24, H, 4.38, N, 0.00. Found: C, 77.99, H, 4.29, N, 0.02.

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Example 35.

Acetic acid 3-Benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester

Prepared from 3-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 17) according to the procedure of Example 34. White solid: mp 122-124°C: MS (EI):
20 [M+], 368; Anal. Calc. for C₂₄H₁₆O₂S: C, 78.24, H, 4.38, N, 0.00. Found: C, 77.47, H, 4.19, N, 0.27.

Example 36.

Acetic acid 2-Acetoxy-4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester

25 Prepared from 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol (Example 18) according to the procedure of Example 34. White solid: mp 179-180°C: MS (EI): [M+], 426; Anal. Calc. for C₂₆H₁₈O₄S: C, 73.22, H, 4.25, N, 0.00. Found: C, 73.17, H, 4.30, N, 0.12.

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Example 37.**4-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol acetate (ester)**

A solution of bromine (0.35 mL, 6.63 mmol) in dichloromethane (10 mL) was added dropwise over a 15 min. period to a stirred, -20°C solution of 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol acetate (ester) (2.22 g, 6.03 mmol) in dichloromethane (45 mL). This solution was stirred for 1.5 h then quenched with dilute aqueous sodium thiosulfate. The organic solvents were removed, water was added and the resulting solid was filtered, washed with water, triturated with pet. ether and dried in vacuo to provide the title compound as a white solid (2.60, 96%):
mp: 204-205°C; NMR (CDCl₃); δ 8.35 (ddd, J = 8, 1, 1 Hz, 1H), 7.81 (ddd, J = 8, 1, 1 Hz, 1H), 7.68-7.61 (m, 2H), 7.47-7.36 (m, 6H), 7.08 (ddd, J = 8, 8, 1 Hz, 1H), 6.69 (ddd, J = 8, 1, 1 Hz, 1H), 2.42 (s, 3H, CH₃); MS (EI): [M⁺], 1 bromine isotope pattern, 446 (60%, MI), 448 (65%, MI), 404 (100%), 406 (95%); Anal. Calc. for C₂₄H₁₅BrO₂S: C, 64.44, H, 3.38, N, 0.00. Found: C, 64.18, H, 3.34, N, -0.03.

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Example 38.**Acetic acid 3-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester**

Prepared from acetic acid 3-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (Example 35) according to the procedure of Example 37. White solid: mp 74-76°C; MS (EI): [M⁺], 1 bromine isotope pattern, 446, 448; Anal. Calc. for C₂₄H₁₅BrO₂S: C, 64.44, H, 3.38, N, 0.00. Found: C, 63.77, H, 3.08, N, 0.12.

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Example 39.**Acetic acid 2-Acetoxy-4-(6-bromo-benzo[b]naphtho [2,3-d]thiophen-11-yl)-phenyl ester**

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Prepared from acetic acid 2-acetoxy-4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (Example 36) according to the procedure of Example 37. White solid: mp 178-179°C; MS (EI): [M⁺], 1 bromine isotope pattern, 504, 506; Anal. Calc. for C₂₆H₁₇BrO₄S: C, 61.79, H, 3.39, N, 0.00. Found: C, 61.37, H, 3.32, N, 0.11.

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Example 40.**4-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenol**

A solution of bromine (0.185 mL, 3.50 mmol) in dichloromethane (7 mL) was added dropwise over a 40 minute period to a solution of 4-(6-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenol (1.31 g, 3.18 mmol) in dichloromethane (26 mL) at -20°C under a dry nitrogen atmosphere that was stirred in the absence of light. After 15 minutes, a dilute aqueous sodium bisulfite solution was added and the reaction mixture was partitioned between water and ether. The ether phase was washed with brine and concentrated to provide the title compound as a white solid (1.65 g, 100%): mp: 189-190°C; NMR (CDCl₃); δ 8.35 (ddd, J = 8, 1, 1, 1H), 7.80 (ddd, J = 8, 1, 1 Hz, 1H), 7.74 (ddd, J = 8, 1, 1 Hz, 1H), 7.65 (ddd, J = 8, 8, 1, 1H), 7.45 (ddd, J = 8, 8, 1 Hz, 1H), 7.37 (ddd, J = 8, 8, 1 Hz, 1H), 7.08 (s, 2H), 7.06 (ddd, J = 8, 8, 1 Hz, 1H), 6.68 (ddd, J = 8, 1, 1 Hz, 1H), 5.03 (s, 1H), 3.31 (septuplet, J = 7 Hz, 2H), 1.29 (d, J = 7 Hz, 6H), 1.26 (d, J = 7 Hz, 6H); MS (EI): 488 (90%), 490 (100); Anal. Calc. for C₂₈H₂₅BrOS: C, 68.71, H, 5.15, N, 0.00. Found: C, 67.74, H, 5.02, N, 0.07.

Example 41.**4-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

Aqueous potassium hydroxide (6.0 mL, 6.0 mmol) was added to a stirred, room temperature suspension of 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol acetate (ester) (2.60 g, 5.81 mmol) in THF (20 mL) / methanol (15 mL). Dissolution occurred immediately and the reaction mixture turned green. After 1h, the organic solvents were removed, water was added, the reaction mixture was acidified with 10% HCl and the resulting solid was washed with water and triturated with pet. ether and then dried in vacuo to provide the title compound as a white solid (2.18 g, 93%). A portion of this solid (0.5 g) was recrystallized from acetic acid /water and then cyclohexane / acetonitrile: mp: 211-213°C; NMR (CDCl₃); δ 8.34 (ddd, J = 8, 1, 1 Hz, 1H), 7.80 (ddd, J = 8, 1, 1 Hz, 1H), 7.67-7.62 (m, 2H), 7.43 (ddd, J = 8, 8, 1 Hz, 1H), 7.39 (ddd, J = 8, 8, 1 Hz, 1H), 7.27 (d, J = 9 Hz, 2H), 7.12 (d, J = 9 Hz, 2H), 7.11

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(m, 1H), 6.78 (ddd, J = 8, 1, 1 Hz, 1H) 4.99 (s, 1H, OH); MS (EI): [M+], 1 bromine isotope pattern, 404 (100%, MI), 406 (96%, MI); Anal. Calc. for C₂₂H₁₃BrOS: C, 65.19, H, 3.23, N, 0.00. Found: C, 64.87, H, 3.00, N, 0.03.

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Example 42.**3-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

Prepared from acetic acid 3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (Example 38) according to the procedure for Example 41. White solid: mp 110-111°C: NMR (CDCl₃); δ 8.35 (dd, J = 8, 1 Hz, 1H), 7.81 (d, J = 8, Hz, 1H), 7.67-7.63 (m, 2H), 7.53 (dd, J = 8, 7 Hz, 1H), 7.44 (ddd, J = 8, 7, 1 Hz, 1H), 7.39 (ddd, J = 8, 7, 1 Hz, 1H), 7.13-7.09 (m, 2H), 7.00 (dd, J = 8, 1 Hz, 1H), 6.88 (dd, J = 1, 1 Hz, 1H), 6.78 (dd, J = 8, 1 Hz, 1H), 4.99 (s, 1H, OH); MS (EI): [M+], 1 bromine isotope pattern, 404 (95%), 406 (100%); Anal. Calc. for C₂₂H₁₃BrOS: C, 65.19, H, 3.23, N, 0.00. Found: C, 64.85, H, 3.51, N, 0.43.

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Example 43.**4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol**

Prepared from acetic acid 2-acetoxy-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (Example 39) according to the procedure for Example 41. White solid: mp 181-182°C: MS (EI): [M+], 1 bromine isotope pattern, 420 (95%); Anal. Calc. for C₂₂H₁₃BrO₂S: C, 62.72, H, 3.11, N, 0.00. Found: C, 62.11, H, 3.10, N, 0.13.

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Example 44.**11-(4-Hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene-6-carbonitrile**

A suspension of 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol acetate (ester) (2.0 g, 4.47 mmol), copper (I) cyanide (2.0 g, 22.3 mmol) and N-methylpyrrolidinone (10 mL) was heated in a sealed vessel in a 150°C oil bath for 9 h. The reaction mixture was cooled to room temperature, added to water and extracted with ethyl acetate. The aqueous phase was filtered and the resulting solid was taken

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up in THF. The THF and ethyl acetate phases were combined and concentrated. THF (100 mL), methanol (50 mL) and aqueous potassium hydroxide (1.0 N, 4.5 mL, 4.5 mmol) were added to the residue. After 5 minutes, water was added and the reaction mixture was acidified with 10% HCl and the resulting solid was filtered, washed with water and triturated with ether (3X) and then pet. ether. The solid was dried in vacuo to provide the title compound as a tan solid (1.27 g, 82%): mp: 307-309°C; NMR (CDCl₃); δ 8.35 (ddd, J = 8, 1, 1 Hz, 1H), 7.84 (ddd, J = 8, 1, 1 Hz, 1H), 7.76-7.69 (m, 2H), 7.51 (ddd, J = 8, 8, 1 Hz, 1H), 7.44 (ddd, J = 8, 8, 1 Hz, 1H), 7.27 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 7.14 (m, 1H), 6.82 (ddd, J = 8, 1, 1 Hz, 1H), 5.08 (s, 1H); IR (KBr, cm⁻¹): 2210 (CN); MS (EI): [M⁺], 451(40%, MI); Anal. Calc. for C₂₃H₁₃NOS: C, 78.61, H, 3.73, N, 3.99. Found: C, 77.84, H, 3.46, N, 3.89.

Example 45.

Methanesulfonic acid 4-Benzo[b]naphtho[2,3-d]thiophen-11-yl-phenyl Ester

Methylsulfonyl chloride (0.63 mL, 8.14 mmol) was added dropwise to a cold (ice bath) solution of 4-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol (2.00 g, 5.43 mmol) in dry methylene chloride (10 mL) and pyridine (2.08 mL). After stirring at ambient temperature for ca. 36 h. the reaction mixture was combined with water (100 mL). The organics were extracted with ether (100 mL), washed with 10% HCl (100 mL) and concentrated to give the title compound as a white solid (2.51 g, 100%); mp 136-139°C; NMR (CDCl₃); δ 8.38 (s, 1H), 7.97 - 7.95 (m, 1H), 7.80 - 7.78 (m, 1H), 7.60 - 7.50 (m, 6H), 7.43 - 7.35 (m, 2H), 7.07 (ddd, J = 8, 7, 1 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 3.33 (s, 3H); MS (EI): [M⁺] 404(100%); Anal. calc. for C₂₃H₁₆O₃S₂ + 0.07 C₆H₁₄, C, 68.52, H, 4.17, N, 0.03. Found: C, 67.91, H, 3.85, N, 0.06.

Example 46.

Methanesulfonic acid 4-(6-Chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester

To a solution of methanesulfonic acid 4-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenyl ester (1.00 g, 2.47 mmol) in chloroform (10 mL) was added sulfonyl chloride (0.21 mL, 2.60 mmol, 1.05 eq) dropwise at room temperature under a dry

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nitrogen atmosphere. After stirring 19 hours the reaction mixture was added to water (100 mL) and the organics were extracted with ether (2x100 mL). The extracts were combined, washed with brine, combined with silica gel and the solvent was removed. The adsorbate was flash chromatographed (85/15 petroleum ether/ethyl acetate) to give the title compound as a white solid (0.957 g, 88%): mp 155-158°C; NMR (CDCl₃); δ 8.41 (ddd, J=8,1,1 Hz, 1H), 7.82 (ddd, J=8,1,1 Hz, 1H), 7.67 (ddd, J=8,7,1 Hz, 1H), 7.61-7.56 (m, 3H), 7.51-7.45 (m, 3H), 7.42-7.38 (ddd, J=8,7,1 Hz, 1H), 7.10 (ddd, J=8,7,1 Hz, 1H), 6.64 (d, J=8 Hz, 1H), 3.34 (s, 3H); MS (+EI) : [M+], 1 chlorine isotope pattern, 438 (100%) , 440 (40%); Anal. Calc. for C₂₃H₁₅ClO₃S₂: C, 62.93, H, 3.49, N, 0.00. Found: C, 62.72, H, 3.25, N, 0.03.

Example 47.

Methanesulfonic acid 4-(6-Iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester

To a solution of methanesulfonic acid 4-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenyl ester (2.24 g, 5.54 mmole) in tetrahydrofuran (22.4 mL), 80% aqueous acetic acid (11.2 mL) and sulfuric acid (0.6 mL) was added iodine (0.984 g, 3.87 mmol) and iodic acid (0.244 g, 1.39 mmol). The reaction mixture was stirred for 88 h at room temperature then combined with an aqueous solution of sodium bisulfite (100 mL). The organics were extracted with ether (500 mL). The extracts were concentrated and chased with benzene and pet ether to provide the title compound as a yellow solid (2.75 g, 94%): mp 176-186°C; NMR (CDCl₃); δ 8.24 (ddd, J = 8, 1, 1 Hz, 1H), 7.81 (ddd, J = 8, 1, 1 Hz, 1H), 7.65 - 7.58 (m, 3H), 7.52 - 7.38 (m, 5H), 7.11 - 7.07 (ddd, J = 8, 7, 1 Hz, 1H), 6.57 (ddd, J = 8, 1, 1 Hz, 1H), 3.33 (s, 3H); MS (+FAB): [M+] m/z 530 (65%), [M + H]⁺ m/z 531 (25%); Anal. calc. for C₂₃H₁₅IO₃S₂: C, 52.08, H, 2.85, N, 0.00. Found: C, 51.75, H, 2.75, N, 0.06.

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Example 48.**Methanesulfonic acid 4-(6-trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester**

A mixture of freshly activated copper (0.359 g, 5.66 mmol) and bis (trifluoromethyl)mercury (0.993g, 3.78 mmol) in N,N-dimethylacetamide (12 mL) was heated at 144°C under a dry nitrogen atmosphere for 2 hours with stirring. After cooling a solution of methanesulfonic acid 4-(6-iodo-benzo[b]naphtho[2,3-d]-thiophen-11-yl)-phenyl ester (1.00g, 1.89 mmol) in N,N-dimethylacetamide (12 mL) was added and the mixture was heated at 160-168°C for 3 hours 20 min. After cooling the mixture was poured into water and the organics were extracted with ether (2 x 200 mL). The extracts were combined, silica gel (ca. 30 mL) was added and the solvent was removed. The adsorbate was flash chromatographed (eluant: 80 : 20 pet ether : ethyl acetate) to provide the title compound as a white solid (0.697 g, 85%): mp 215 - 216°C; NMR (CDCl₃); δ 8.39 - 8.36 (m, 1H), 7.81 - 7.79 (m, 1H), 7.71 - 7.67 (m, 1H), 7.61 - 7.59 (m, 3H), 7.51 - 7.46 (m, 3H), 7.41 (ddd, J = 8, 7, 1 Hz, 1H), 7.08 (ddd, J = 8, 7, 1 Hz), 6.54 (d, J = 8 Hz, 1H), 3.35 (s, 3H); MS +FAB [M+H]⁺ m/z 473 and m+ 472; Anal. Calc. for C₂₄H₁₅F₃O₃S₂·0.15C₆H₆: C, 61.76, H, 3.31, N, 0.00. Found: C, 61.20, H, 3.11, N, 0.16.

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Example 49.**Methanesulfonic acid 4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester**

A suspension of methanesulfonic acid 4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (1.65g, 3.11 mmole), tetramethyltin (3.58, 25.8 mmole), and bis(triphenylphosphine)palladium II chloride (0.218g, 0.311 mmole 10 mole %) in dry N,N dimethylformamide (16mL) was heated in a sealed vessel under argon at 103°C for 4 hours and left at room temperature overnight. The reaction mixture was added to water (200 mL) and extracted with ether. Silica gel (40mL) was added and the solvent removed. The adsorbate was flash chromatographed (85 : 15 Petroleum ether : ethyl acetate) to give the title compound as a pale yellow solid (1.12 g, 86%): mp 172-173°C; NMR (CDCl₃); δ 8.18 (ddd, J = 8, 1, 1Hz, 1H), 7.81

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(ddd, J = 1, 1, 8 Hz, 1H), 7.62-7.55 (m, 3H), 7.50 - 7.48 (m, 2H), 7.44 - 7.34(m, 2H), 7.06 (ddd, J = 8, 7, 1Hz, 1H), 6.64 (ddd, J = 8,1, 1Hz), 3.32(s, 3H), 2.99 (s, 3H); MS: EI [m/z] 418(100%); Anal. Calcd. for C₂₄H₁₈O₃S₂: C, 68.87, H, 4.34, N, 0.00. Found: C, 68.60, H, 4.26, N, 0.02.

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Example 50.**4-(6-Chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

A biphasic mixture of methanesulfonic acid 4-(6-chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (0.917 g, 2.09 mmol) in dioxane (13 mL) and a solution of sodium hydroxide (2.5 N, 6.7 mL, 16.7 mmol, 8 eq) was heated at reflux overnight. After cooling to room temperature the reaction mixture was combined with water (50 mL), acidified with concentrated hydrochloric acid, and stirred for 15 minutes. The crude white solid product was collected by filtration, redissolved in ether, combined with silica gel, and the solvent was removed. The adsorbate was flash chromatographed (gradient 85/15-80/20 petroleum ether/ethyl acetate) to give the title compound as a white solid (0.705 g, 94%); mp 193-195°C; NMR (CDCl₃); δ 8.37 (ddd, J = 8, 1, Hz, 1H), 7.81 (ddd, J = 8, 1, 1 Hz, 1H), 7.68-7.63 (m, 2H), 7.44 (ddd, J = 8, 7, 1 Hz, 1H), 7.39 (ddd, J = 8, 7, 1 Hz, 1H), 7.29-7.26 (m, 2H), 7.14-7.09 (m, 3H), 6.81 (ddd, J = 8, 1, 1 Hz, 1H), 5.01 (d, J = 4 Hz, 1H); MS (+EI): [M⁺], 1 chlorine isotope pattern, 360 (100%), 362 (45%); Anal. calc. for C₂₂H₁₃ClO: C, 73.23, H, 3.63, N, 0.00. Found: C, 72.86, H, 3.24, N, 0.04.

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Example 51.**4-(6-Iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

To a solution of methanesulfonic acid 4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (1.00 g, 1.89 mmol) in tetrahydrofuran (5 mL) was added a 2.5 N aqueous solution of sodium hydroxide (6.0 mL) and the biphasic reaction mixture was heated at reflux for 5 hours and then heated in a sealed pressure tube at 110°C for about 18 hours. The reaction mixture was diluted with water (100 mL), acidified with 10% hydrochloric acid and the organics were extracted with ether

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(2x100 mL). The extracts were combined, washed with water (100 mL), concentrated and chased with petroleum ether to give the title compound (0.869 g, over theoretical); NMR (DMSO-d₆); δ 9.85 (s, 1H, OH), 8.15 (d, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 7.73 (ddd, J = 8, 7, 1 Hz, 1H), 7.69-7.44 (m, 3H), 7.21-7.16 (m, 3H),
5 7.09-7.06 (m, 2H), 6.68 (d, J = 8 Hz, 1H).

Example 52.**4-(6-Trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

Prepared from methanesulfonic acid 4-(6-trifluoromethyl-benzo[b]naphtho-
10 [2,3-d]thiophen-11-yl)-phenyl ester (Example 48) according to the procedure of Example 51. White solid: mp 210 -211°C; NMR (CDCl₃); δ 8.35 (m, 1H), 7.80 - 7.77 (m, 1H), 7.72 - 7.64 (m, 2H), 7.47 (ddd, J = 8, 7, 1 Hz, 1H), 7.39 (ddd, J = 8, 7, 1 Hz, 1H), 7.28 - 7.24 (m, 2H), 7.16 - 7.08 (m, 3H), 6.75 (d, J = 8 Hz, 1H), 5.03 (s, 1H); MS: (+) EI (direct probe) [M⁺]: 394 (100%); Anal. Calc. for: C₂₃H₁₃F₃OS: C,
15 70.04, H, 3.32, N, 0.00. Found: C, 69.68, 3.12, N, 0.10.

Example 53.**4-(6-Methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

Prepared from methanesulfonic acid 4-(6-methyl-benzo[b]naphtho[2,3-d]thio-
20 phen-11-yl)-phenyl ester (Example 49) according to the procedure of Example 51. White solid: mp 184-185°C; NMR (CDCl₃); δ 8.16 (ddd, J = 8, 1, 1 Hz, 1H), 7.81 (ddd, J = 8, 1, 1 Hz, 1H), 7.67 (ddd, J = 8, 1, 1 Hz, 1H), 7.58 (ddd, J = 8, 7, 1 Hz, 1H), 7.42-7.34 (m, 2H), 7.29 - 7.26 (m, 3H), 7.12-7.06 (m, 3H), 6.82 (ddd, J = 8, 1, 1 Hz, 1H), 4.94(s, 1H), 2.98 (s, 3H); MS(EI): [M⁺], 340(100%); Anal. Calcd. for C₂₃H₁₆OS: C,
25 81.14, H, 4.74, N, 0.00, Found C, 81.47, H, 4.59, N, 0.02.

Example 54.**4-(6-Methoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

To cold (ice bath) anhydrous methanol (13.2 mL) was added sodium hydride
30 (80% by weight suspension in mineral oil, 1.70 g, 56.6 mmol) in three portions. After

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stirring in the cold for 0.5 hours and at ambient temperature for 50 minutes copper II chloride (0.251 g, 1.87 mmol) and solution of methanesulfonic acid 4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (3.00 g, 5.66 mmol) in dry N,N-dimethylformamide (24 mL) were added. The reaction mixture was heated at reflux
5 for approximately 3 hours, cooled to room temperature, diluted with water (400 mL), acidified with 10% hydrochloric acid and extracted with diethyl ether. The extracts were combined, silica gel was added and the solvent removed. The adsorbate was flash chromatographed (40/60 petroleum ether/methylene chloride) to provide the title compound as a white solid (1.82 g, 90%): mp 218-223°C (dec); NMR (CDCl₃); δ
10 8.27 (ddd, J = 8, 1, 1 Hz, 1H), 7.80 (ddd, J = 8, 1, 1 Hz, 1H), 7.65 (ddd, J = 8, 1, 1 Hz, 1H), 7.57 (ddd, J = 8, 7, 1 Hz, 1H), 7.40 (ddd, J = 8, 7, 1 Hz, 1H), 7.36 (ddd, J = 8, 7, 1 Hz, 1H), 7.30-7.26 (m, 2H), 7.13-7.07 (m, 3H), 6.85 (ddd, J = 8, 1, 1 Hz, 1H), 4.98 (s, 1H), 4.21 (s, 3H); MS (EI): [M⁺], 356 (100%); Anal. Calc. for C₂₃H₁₆O₂S: C, 77.50, H, 4.52, N, 0.00; Found C, 76.79, H, 4.61, N, 0.11.

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Example 55.**4-(6-Phenylsufanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

Sodium hydroxide (0.183 g, 4.58 mmol) was added to a stirred, room temperature solution of methanesulfonic acid 4-(6-iodo-benzo[b]naphtho[2,3-d]-
20 thiophen-11-yl)-phenyl ester (1.04 g, 1.95 mmol), thiophenol (0.47 mL, 4.578 mmol), copper (I) oxide (0.326 g, 2.28 mmol) and dimethylformamide (20 mL). The vessel was heated in a 155-160°C oil bath under an argon atmosphere. After 7h, the reaction mixture was cooled to room temperature, added to water, acidified with 10% HCl and extracted with ether. The ether extract was filtered to remove copper salts and silica
25 gel was added. The solvent was removed and the adsorbate was flash chromatographed (eluent: gradient: 9:1 to 85:15 petroleum ether: ethyl acetate) to provide the title compound as a white solid (0.721 g, 86%): mp 162-164°C; NMR (DMSO-d₆); δ 9.87 (s, 1H), 8.48 (ddd, J = 8, 1, 1 Hz, 1H), 7.95 (ddd, J = 8, 1, 1 Hz, 1H), 7.66 (m, 2H), 7.52 (ddd, J = 8, 7, 1 Hz, 1H), 7.44 (ddd, J = 8, 7, 1 Hz, 1H), 7.27-

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7.07 (m, 10H), 6.76 (d, J = 8 Hz, 1H); MS (EI): 434 (M⁺, 100%); Anal. Calc. for C₂₈H₁₈OS: C, 77.39, H, 4.19, N, 0.00. Found: C, 76.82, H, 3.95, N, 0.16.

Example 56.

5 4-[6-(2-Dimethylamino-ethylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol

To a suspension of methanesulfonic acid 4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (1.00 g, 1.89 mmol), dimethylaminoethanethiol hydrochloride (0.614 g, 4.34 mmol, 2.3 eq) and copper I oxide (0.316 g, 8.69 mmol, 1.17 eq) in anhydrous N,N-dimethylformamide (24 mL) was added finely ground
10 sodium hydroxide (0.348 g, 8.69 mmol, 4.6 eq) at room temperature in a pressure vessel. The vessel was flushed with argon, sealed and heated with stirring at 155°C (oil bath) for 6 hours and at ambient temperature for 12 hours. The reaction mixture was poured into water (100 mL) and extracted with ether. The solid which remained as a suspension in the aqueous phase was filtered. The filtrate was extracted once
15 more with ether. The extracts were combined and silica gel was added. The solvents were removed and the adsorbate was flash chromatographed (gradient 94/6 - 95/ 5) methylene chloride: isopropanol to give the title compound as a solid (0.707 g, 87%):
NMR (DMSO-d₆); δ 9.83 (s, 1H, OH), 8.65 (d, J = 8 Hz, 1H), 7.98 (d, J = 8 Hz, 1H), 7.71 (ddd, J = 8, 7, 1 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.50 (ddd, J = 8, 7, 1 Hz, 1H),
20 7.43 (ddd, J = 8, 7, 1 Hz, 1H), 7.21-7.05 (m, 3H), 7.08-7.04 (m, 2H), 6.73 (d, J = 8 Hz, 1H), 3.35-3.27 (m,), 3.10 (t, J = 6 Hz, 2H), 2.21-2.08 (broad singlet, 6H); MS(EI): [M⁺] 429.

Example 57.

25 4-[6-(Pyridin-4-ylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol

To a suspension of methanesulfonic acid 4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (1.00 g, 1.89 mmol), 4 mercaptopyridine (0.614 g, 4.34 mmol, 2.3 eq) and copper I oxide (0.316 g, 2.21 mmol, 1.17 eq) in dry N,N-dimethylformamide (24 mL) was added finely ground sodium hydroxide (0.174 g,
30 4.34 mmol, 2.3 eq) and the mixture was heated in a pressure bottle at 157°C (oil bath)

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under argon for 5 hours and then stirred at ambient temperature overnight. The reaction mixture was poured into water (100 mL) and the organics were extracted with ether (2.300 mL). The extracts were combined, dried with brine, and silica gel was added. The solvent was removed and the adsorbate was flash chromatographed (97/3 methylene chloride/isopropanol) to give a solid which was stirred in water (100 mL) overnight and collected on a sintered glass funnel and air dried to give the title compound as a solid (0.587 g, 73%); NMR (DMSO-d₆); δ 9.90 (s, 1H), 8.37 (d, J = 8 Hz, 1H), 8.30 (d, J = 5 Hz, 2H), 7.95 (d, J = 8 Hz, 1H), 7.70 (m, 2H), 7.57 (m, 1H), 7.45 (t, J = 8 Hz, 1H), 7.28 (d, J = Hz, 2H), 7.20 (t, J = 8 Hz, 1H), 7.11 (d, J = 8 Hz, 2H), 6.96 (d, J = 6 Hz, 2H), 6.77 (d, J = 8 Hz, 1H); MS (EI): [M+] 435.

Example 58.

11-(3, 5-Dibromo-4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene-6-carbonitrile

A solution of bromine (0.21 mL, 4.07 mmol) in acetic acid (3 mL) was added dropwise to a room temperature, stirred suspension of 11-(4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene-6-carbonitrile (650 mg, 1.85 mmol), potassium acetate (1.82 g, 18.5 mmol) and acetic acid (17 mL). After 35 minutes, water (100 mL) and a small amount of solid sodium sulfite were added. The suspension was filtered and the solid was washed with water, triturated with pet. ether and dried in vacuo to provide the title compound as a tan solid (1.04 g, 96%); mp 321-323°C: NMR (CDCl₃); δ 8.36 (ddd, J = 8, 1, 1 Hz, 1H), 7.87 (ddd, J = 8, 1, 1 Hz, 1H), 7.76 (ddd, J = 8, 7, 1 Hz, 1H), 7.67 (ddd, J = 8, 1, 1 Hz, 1H), 7.56 (ddd, J = 8, 7, 1 Hz, 1H), 7.54 (s, 2H), 7.50 (ddd, J = 8, 7, 1 Hz, 1H), 7.27 (ddd, J = 8, 7, 1 Hz, 1H), 6.90 (ddd, J = 8, 1, 1 Hz, 1H), 6.24 (s, 1H, OH); MS (EI): [M+], 2 bromine isotope pattern, 507 (55%), 509 (100%), 511 (55%); Anal. Calc. for C₂₃H₁₁Br₂NOS·0.5 H₂O: C, 53.31, H, 2.33, N, 2.70. Found: C, 53.51, H, 2.28, N, 2.70.

The compounds in Examples 59-66 were prepared using the procedure in Example 58 and the appropriate starting material.

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Example 59.**2,6-Dibromo-4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

From 4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 51).
White solid: mp 221-222°C; NMR (CDCl₃); δ 8.22 (d, J = 8 Hz, 1H), 7.83 (d, J = 8
5 Hz, 1H), 7.63 (ddd, J = 8, 7, 1 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 7.54 (s, 2H), 7.50-7.43
(m, 2H), 7.20 (ddd, J = 8, 7, 1 Hz, 1H), 6.83 (d, J = 8 Hz, 1H); MS (+FAB): [M⁺], 2
bromine isotope pattern, 608 (25%), 609.7 (100%), 612 (35%); Anal. Calc. for
C₂₂H₁₁Br₂IOS: C, 43.31, H, 1.82, N, 0.00. Found: C, 42.98, H, 1.93, N, 0.26.

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Example 60.**2,6-Dibromo-4-(6-chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

From 4-(6-chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example
50). White solid: mp 222-223°C; NMR (CDCl₃); δ 8.39 (ddd, J=8,1,1 Hz, 1H), 7.84
(ddd, J = 8, 1, 1 Hz, 1H), 7.67 (ddd, J = 8, 7, 1 Hz, 1H), 7.61 (ddd, J = 8, 1, 1 Hz, 1H),
15 7.55 (s, 2H), 7.52-7.43 (m, 2H), 7.23 (ddd, J = 8, 7, 1 Hz, 1H), 6.89 (ddd, J = 8, 1, 1
Hz, 1H), 6.19 (s, 1H); MS (EI): [M⁺], 2 bromine, 1 chlorine isotope pattern, 516
(38%), 518 (100%), 520 (72%), 521 (20%); Anal. Calc. for C₂₂H₁₁Br₂ClOS: C,
50.95, H, 2.14. Found: C, 51.12, H, 2.20.

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Example 61.**2,6-Dibromo-4-(6-trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

From 4-(6-trifluoromethyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol
(Example 52). White solid: mp 223-225°C; NMR (CDCl₃); δ 8.37 (ddd, J = 8, 1, 1
Hz, 1H), 7.82 (m, 2H), 7.54 - 7.50 (m, 2H), 7.53 (s, 2H), 7.45 (ddd, J = 8, 7, 1 Hz,
25 1H), 7.20 (ddd, J = 8, 7, 1 Hz, 1H), 6.83 (d, J = 8 Hz, 1H), 6.22 (s, 1H, OH); MS:
(+)EI (direct probe) [M⁺], 2 bromine isotope pattern, 550 (52%), 552 (100%) 554
(58%); Anal. Calc. for C₂₃H₁₁Br₂F₃OS: C, 50.03, H, 2.01, N, 0.00. Found: C, 49.66,
H, 2.07, N, 0.08.

Example 62.**2,6-Dibromo-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

From 4-methyl[b]naphtho[2,3-d]thiophen-11-yl-phenol (Example 53). White solid: mp 224-226°C: NMR (CDCl₃); δ 8.17 (ddd, J = 8, 1, 1 Hz, 1H), 7.84 (ddd, J = 8, 1, 1 Hz, 1H), 7.62 - 7.58 (m, 2H), 7.55 (s, 2H), 7.47 - 7.39 (m, 3H), 7.18 (ddd, J = 8, 7, 1 Hz, 1H), 6.89 (ddd, J = 8, 1, 1 Hz, 1H), 6.16 (s, 1H); MS (-ESI): m/z 495.2 (40%), 497.1 (100%), 499.2 (27%); Anal. Calc. for C₂₃H₁₄Br₂OS: C, 55.45, H, 2.83, N, 0.00. Found: C, 56.17, H, 2.78, N, 0.13.

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Example 63.**2,6-Dibromo-4-(6-methoxybenzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

From 4-(6-methoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 54). White solid: mp 233-234°C; NMR (DMSO-d₆); δ 10.35 (broad s, 1H), 8.23 (d, J = 8 Hz, 1H), 8.03 (d, J = 8 Hz, 1H), 7.69 - 7.64 (m, 1H), 7.64 (s, 2H), 7.54 (d, J = 4 Hz, 2H), 7.48 (ddd, J = 8, 7, 1 Hz, 1H), 7.26 (ddd, J = 8, 7, 1 Hz, 1H), 6.84 (d, J = 8 Hz, 1H), 4.13 (s, 3H); MS (EI): [M⁺], 2 bromine isotope pattern, 512 (48%), 514 (100%), 516 (54%); Anal. Calc. for C₂₃H₁₄Br₂O₂S: C, 53.72, H, 2.74, N, 0.00. Found: C, 53.62, H, 2.55, N, 0.18.

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Example 64.**2,6-Dibromo-4-(6-phenylsulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

From 4-(6-phenylsulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 55). White solid: mp 152-155°C: NMR (DMSO-d₆); δ 10.42 (s, 1H), 8.49 (d, J = 8 Hz, 1H), 7.99 (d, J = 8 Hz, 1H), 7.75 (s, 2H), 7.69 (ddd, J = 8, 7, 1 Hz, 1H), 7.63 (d, J = 8 Hz, 1H), 7.57 (ddd, J = 8, 7, 1 Hz, 1H), 7.48 (ddd, J = 8, 7, 1 Hz, 1H), 7.28 (ddd, J = 8, 7, 1 Hz, 1H), 7.25-7.21 (m, 2H), 7.14 (ddd, J = 8, 7, 1 Hz, 1H), 7.09 (d, J = 8 Hz, 2H), 6.81 (d, J = 8 Hz, 1H), 1.90 (s, 3H, AcOH); MS (EI): [M⁺], 2 bromine isotope pattern, 590 (50%), 592 (100%), 594 (60%); Anal. Calc. for C₂₈H₁₆Br₂OS₂• 1.0 CH₃CO₂H• 0.5 H₂O: C, 54.48, H, 3.20, N, 0.00. Found: C, 54.56, H, 2.91, N, 0.23.

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Example 65.**2,6-Dibromo-4-[6-(pyridin-4-ylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol**

5 From 4-[6-(pyridin-4-ylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol (Example 57). Yellow solid : mp 225-270°C (dec); NMR (DMSO-d₆); δ 10.48 (s, 1H, -OH), 8.40 (dd, J = 8, 1 Hz, 2H), 8.37 (d, J = 8 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 7.76 (s, 2H), 7.75-7.68 (m, 2H), 7.62 (ddd, J = 8, 7, 1 Hz, 1H), 7.50 (ddd, J = 8, 7, 1 Hz, 1H), 7.31 (ddd, J = 8, 7, 1 Hz, 1H), 7.20 (dd, J = 6, 1 Hz, 2H), 6.83 (d, J = 8 Hz, 1H); Anal. Calc. for C₂₇H₁₅Br₂NOS₂: C, 54.65, H, 2.55, N, 2.36. Found: C, 48.94, H, 2.46, N, 2.22.

Example 66.**2,6-Dibromo-4-[6-(2-dimethylaminoethylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol**

15 From 4-[6-(2-dimethylaminoethylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol (Example 56). Yellow solid : NMR (DMSO-d₆); δ 8.65 (d, J = 8 Hz, 1H), 8.04 (d, J = 8 Hz, 1H), 7.77 (septet, J = 3 Hz, 1H), 7.65 (s, 2H), 7.60-7.58 (m, 2H), 7.50 (dd, J = 8, 1 Hz, 1H), 7.27 (ddd, J = 8, 7, 1 Hz, 1H), 6.86 and 6.63 (s, isomers, 2H), 6.79 (d, J = 8 Hz, 1H), 3.24 (d, m, 2H), 2.85 (m, 2H); MS (EI): [M⁺], 2 bromine isotope pattern, 585 (3%), 587 (7%), 589 (4%).

Example 67.**2,6-Dichloro-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol**

25 Methanol (20 mL) was purged with chlorine gas for 2 min. This solution was cooled to -78°C and added to a -78°C solution of 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (0.609 g, 1.50 mmol) in methanol (15 mL). After 25 min, the solution was added to a rapidly stirred biphasic mixture of dilute aqueous sodium thiosulfate and ether. The layers were separated and silica gel was added to the ether phase. The ether was removed and the adsorbate was flashed (gradient: 9:1 to 1:1

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petroleum ether:ethyl acetate). Silica gel was added to the fractions containing the desired product and the solvent was removed. The adsorbate was flashed (9:1 petroleum ether:ethyl acetate). Silica gel was added to the fractions containing the desired product and the solvent was removed. The adsorbate was flash
5 chromatographed (7:3 petroleum ether:dichloromethane) to provide the title compound as a white solid (0.082 g, 12%): NMR (DMSO-d₆); δ 10.65 (s, 1H), 8.28 (ddd, J = 8, 1, 1 Hz, 1H), 8.07 (ddd, J = 8, 1, 1 Hz, 1H), 7.78 (ddd, J = 9, 5, 2 Hz, 1H), 7.63-7.58 (m, 2H), 7.53 (s, 2H), 7.52 (ddd, J = 8, 8, 1 Hz, 1H), 7.31 (ddd, J = 8, 7, 1 Hz, 1H), 6.69 (d, J = 8 Hz, 1H): MS (EI): [M⁺], 1 bromine, 2 chlorine isotope pattern,
10 472 (60%), 474 (100%), 476 (50%).

Example 68.

2-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol

Prepared from 3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol
15 (Example 42) according to the procedure of Example 58. White solid: mp 111-112°C: MS (+FAB): [M⁺], 482; Anal. Calc. for C₂₂H₁₂Br₂OS: C, 54.57, H, 2.50, N, 0.00. Found: C, 53.72, H, 2.35, N, 0.41.

Example 69.

2,4-Dibromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol

Prepared from 3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol
(Example 42) according to the procedure of Example 58. White solid: 269-270°C: MS (+FAB): [M⁺], 560, 562, 564, 566; Anal. Calc. for C₂₂H₁₁Br₃OS: C, 46.93, H, 1.97, N, 0.00. Found: C, 46.43, H, 2.20, N, 0.11.

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Example 70.

3-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol

Prepared from 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol (Example 43) according to the procedure of Example 58. White solid: mp

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212-213°C: MS (EI): [M+], 2 bromine isotope pattern, 498, 500, 502; Anal. Calc. for C₂₂H₁₂Br₂O₂S: C, 52.83, H, 2.42, N, 0.00. Found: C, 52.08, H, 2.55, N, 0.01.

Example 71.

5 4-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol

Prepared from 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol (Example 43) according to the procedure of Example 58. White solid: mp 138-140°C: MS (EI): [M+], 2 bromine isotope pattern, 498, 500, 502; Anal. Calc. for C₂₂H₁₂Br₂O₂S: C, 52.83, H, 2.42, N, 0.00. Found: C, 52.17, H, 2.71, N, 0.05.

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Example 72.

[11-(4-Hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-yloxy]-acetic acid methyl ester

11-(4-Hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-ol (1.36 g, 3.96 mmol), methyl bromoacetate (0.38 mL, 4.01 mmol), potassium carbonate (0.548 g, 3.97 mmol) and N,N-dimethylformamide (21 mL) were combined and stirred at ambient temperatures for 2.5h. The reaction mixture was added to water and extracted with ethyl acetate and THF. Silica gel was added to the organic phase and the solvent was removed. The adsorbate was flash chromatographed (eluent: gradient dichloromethane to 98:2 dichloromethane: acetonitrile) to provide the title compound as a white solid (0.953 g, 58%): mp: 229-231°C: NMR (DMSO-d₆): δ 9.78 (s, 1H), 8.51 (s, 1H), 8.00 (d, J = 8 Hz, 1H), 7.56-7.39 (m, 4H), 7.18 (d, J = 9 Hz, 2H), 7.05 (d, J = 9 Hz, 2H), 6.79 (dd, J = 9, 2 Hz, 1H), 6.66 (d, J = 9 Hz, 1H), 4.86 (s, 2H), 3.68 (s, 3H); MS (EI): 414 (100%, M+); Anal. Calc. for C₂₅H₁₈O₄S: C, 72.45, H, 4.38, N, 0.00. Found: C, 71.78, H, 4.41, N, 0.13.

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Example 73.

[11-(4-Methoxycarbonylmethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-yloxy]-acetic acid methyl ester

30 11-(4-Hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-ol (0.60 g, 1.752 mmol), methyl bromoacetate (0.70 mL, 7.39 mmol), potassium carbonate (1.2 g, 8.76

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mmol) and N,N-dimethylformamide (8 mL) were combined and stirred at ambient temperatures overnight. The reaction mixture was added to water and filtered. The solid was washed with water and dried in vacuo to provide the title compound as a white solid (0.82 g, 96%): mp: 152-154°C: NMR (CDCl₃): δ 8.27 (s, 1H), 7.91 (dt, J = 8, 1 Hz, 1H), 7.61 (dm, J = 8 Hz, 1H), 7.49 (ddd, J = 8, 7, 1 Hz, 1H), 7.39-7.26 (m, 3H), 7.18 (d, J = 9 Hz, 2H), 6.66 (dd, J = 1 Hz, 2H), 4.82 (s, 2H), 4.67 (s, 2H), 3.90 (s, 3H), 3.81 (s, 3H); MS (FAB+): 487 (10%, M+H); Anal. Calc. for C₂₈H₂₂O₆S: C, 69.12, H, 4.56, N, 0.00. Found: C, 67.52, H, 4.40, N, 0.07.

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Example 74.[11-(4-Carboxymethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-yloxy]-acetic acid

1.0 N Aqueous potassium hydroxide (8.0 mL, 8.0 mmol) was added to a stirred suspension of [11-(4-methoxycarbonylmethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-yloxy]-acetic acid methyl ester (0.750 g, 1.54 mmol) in THF (20 mL) and methanol (13 mL). Dissolution occurred. After 3 h at ambient temperature, the reaction mixture was diluted with water and extracted with ether (100 mL). The aqueous phase was acidified with 10% aqueous HCl and filtered. The solid was washed with water and triturated with pet. ether. The solid was dried in vacuo at 70°C to provide a grey solid. This solid was recrystallized from acetic acid to provide the title compound as a white solid (0.502, 71%): mp 220-222°C: NMR (DMSO-d₆): δ 12.8 (broad s, 2H), 8.54 (s, 1H), 8.02 (d, J = 8 Hz, 1H), 7.56-7.40 (m, 4H), 7.31 (d, J = 8 Hz, 2H), 7.23 (d, J = 8 Hz, 2H), 6.73 (dd, J = 9, 1 Hz, 1H), 6.56 (d, J = 9 Hz, 1H), 4.85 (s, 2H), 4.74 (s, 2H), 1.97 (s, 2.49H, 0.83 mol acetic acid); MS (FAB+): 459 (20%, M+H); Anal. Calc. for C₂₆H₁₈O₆S•0.83CH₃CO₂H: C, 65.46, H, 4.24, N, 0.00. Found: C, 64.47, H, 4.05, N, 0.03.

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Example 75.[11-(4-Methoxycarbonylmethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-8-yloxy]-acetic acid, methyl ester

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To a suspension of 11-(4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-8-ol (0.600 g, 1.75 mmol) and potassium carbonate (0.605 g, 4.38 mmol, 2.5 eq) in

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anhydrous N,N-dimethylformamide (3 mL) was added methylbromoacetate (0.50 mL, 5.26 mmol) dropwise at room temperature. After stirring 26 hours additional methylbromoacetate (0.166 mL, 1.75 mmol) was added and stirring continued for 64 hours. The solvents were removed and water (100 mL) was added. The solid was dissolved in a mixture of diethyl ether and methylene chloride and combined with silica gel. The solvents were removed and the adsorbate was flash chromatographed (70/30 petroleum ether/ethyl acetate) to give the title compound as a yellow solid (0.300 g, 35%).

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Example 76.[11-(4-Carboxymethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-8-yloxy]-acetic acid

To a solution of [11-(4-methoxycarbonylmethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-8-yloxy]-acetic acid, methyl ester (0.268 g, 0.551 mmol) in tetrahydrofuran (8 mL) and methanol (5 mL) was added an aqueous solution of potassium hydroxide (1N, 2.2 mL, 2.2 mmol) dropwise at room temperature. After stirring 2 hours an addition of potassium hydroxide (1N, 1 mL, 1 mmol) was introduced. After stirring another 14 hours the solvents were removed and the residue was dissolved in water (50 mL) and was acidified with 10% aqueous hydrochloric acid, and the organics were extracted with diethyl ether. The solvent was removed and chased with benzene and petroleum ether and dried at 53°C to give the title compound as a white solid (0.18 g, 43%): mp 245-246°C; NMR (DMSO-d₆): δ 13.08 (broad s, 2H), 8.44 (s, 1H), 7.93 (d, J = 8 Hz, 1H), 7.45 - 7.35 (m, 3H), 7.31 (d, J = 9 Hz, 2H), 7.22 (d, J = 9 Hz, 2H), 7.17 (dd, J = 3, 9 Hz, 1H), 7.10 (ddd, J = 9, 9, 1 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 4.84 (d, J = 7 Hz, 4H); MS (EI): [M+] 458; Anal. Calc. for C₂₆H₁₈O₆S: C, 68.11, H, 3.96, N, 0.00. Found: C, 66.41, H, 3.95, N, 0.05.

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Example 77.[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid, methyl ester

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2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (1.0 g, 1.78 mmol), methyl bromoacetate (0.35 mL, 3.70 mmol), potassium carbonate

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(0.50 g, 3.62 mmol) and N,N-dimethylformamide (5 mL) were combined and stirred at ambient temperatures overnight. The reaction mixture was added to water and filtered. The solid was washed with water and dried in vacuo to provide the title compound as a white solid (1.11 g, 98%): mp 183-184°C: NMR (CDCl₃); δ 8.36 (ddd, J = 8, 1, 1 Hz, 1H), 7.84 (ddd, J = 8, 1, 1 Hz, 1H), 7.68 (ddd, J = 8, 7, 1 Hz, 1H), 7.62 (s, 2H), 7.57 (ddd, J = 8, 1, 1 Hz, 1H), 7.51 (ddd, J = 8, 7, 1 Hz, 1H), 7.42 (ddd, J = 8, 7, 1 Hz, 1H), 7.18 (ddd, J = 8, 7, 1 Hz, 1H), 6.72 (ddd, J = 8, 1, 1 Hz, 1H), 4.88 (s, 2H), 3.94 (s, 3H); MS (EI): [M⁺], 3 bromine isotope pattern, 632 (30%), 634 (90%) 636 (100%) 638 (35%); Anal. Calc. for C₂₅H₁₅Br₃O₃S: C, 47.27, H, 2.38, N, 0.00. Found: C, 47.17, H, 2.19, N, 0.09.

Example 78.

[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid, tert-butyl ester

To a suspension of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (1.50 g, 2.66 mmol) in anhydrous DMF (10mL) was added potassium carbonate (0.496 g, 3.59 mmol) followed by the dropwise addition of tert-butyl bromoacetate (0.79 mL, 3.59 mmol) at room temperature under a dry nitrogen atmosphere. After stirring for 3 h. the reaction mixture was poured into water (250 mL) and filtered. The white solid was washed with water then taken up in methylene chloride and silica gel was added. The solvent was removed and the silica adsorbate was flash chromatographed (96 : 4 petroleum ether : ethyl acetate) to provide the title compound as a white solid (1.14 g, 64%): NMR (CDCl₃); δ 8.36 (d, J = 8 Hz, 1H, ArH), 7.85 (d, J = 8 Hz, 1H, ArH), 7.67 (ddd, J = 8, 7, 1 Hz, 1H, ArH), 7.60 (s, 2H, ArH), 7.59-7.36 (m, 3H, ArH), 7.19 (t, J = 7 Hz, 1H, ArH), 6.75 (d, J = 7 Hz, 1H, ArH), 4.73 (s, 2H, CH₂), 1.60 (s, 9H, 3(CH₃)); MS (EI): [M⁺], 3 bromine pattern 674 (29%), 676 (85%), 678 (85%), 680 (35%); Anal. Calc. for C₂₈H₂₁Br₃O₃S: C, 49.66, H, 3.12, N, 0.00; found: C, 49.55, H, 2.84, N, 0.06.

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Example 79.**[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid**

1.0 N Aqueous potassium hydroxide (2.66 mL, 2.66 mmol) was added to a stirred suspension of [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid, methyl ester (1.51 g, 2.37 mmol) in THF (13 mL) and methanol (4 mL). Dissolution occurred. After 2.5 h at ambient temperature, the reaction mixture was diluted with water and extracted with ether (100 mL). The aqueous phase was acidified with 10% aqueous HCl and filtered. The solid was washed with water and triturated with pet. ether. The solid was dried in vacuo at 70°C to provide the title compound as a white solid (1.34 g, 91%): mp 259-261°C: NMR (DMSO-d₆): δ 8.29 (dd, J = 8, 1 Hz, 1H), 8.06 (dd, J = 8, 1 Hz, 1H), 7.82 (s, 2H), 7.79 (ddd, J = 8, 6, 2 Hz, 1H), 7.61 (m, 2H), 7.52 (ddd, J = 8, 7, 1 Hz, 1H), 7.32 (ddd, J = 8, 7, 1 Hz, 1H), 6.73 (dd, J = 8, 1 Hz, 1H), 4.78 (s, 2H); MS (EI): [M⁺], 3 bromine isotope pattern, 618 (30%), 620 (90%) 622 (100%) 624 (50%); Anal. Calc. for C₂₄H₁₃Br₃O₃S: C, 46.41, H, 2.11, N, 0.00. Found: C, 46.38, H, 1.99, N, 0.01.

Example 80.**[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid, sodium salt**

Aqueous sodium hydroxide (1.00 N, 0.315 mL, 0.315 mmol) was added to a stirred solution of [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid (194 mg, 0.315 mmol) in THF (1 mL) / methanol (1mL). The reaction mixture was concentrated, water (2.5 mL) was added and the solid was filtered (101 mg). The aqueous phase was extracted with ether (25 mL) and the ether phase was evaporated to dryness to provide a second solid (77 mg). The solids were combined and triturated with toluene and benzene and dried in vacuo to provide the title compound as a tan solid (152 mg, 76%): mp 315-317°C: NMR (DMSO-d₆): δ 8.28 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.79 (ddd, J = 8, 7, 2 Hz, 1H), 7.76 (s, 2H), 7.62 (m, 2H), 7.52 (ddd, J = 8, 8, 1 Hz, 1H), 7.33 (ddd, J = 8, 8, 1 Hz, 1H), 6.69 (d, J = 8 Hz, 1H), 4.27 (s, 2H); MS (-FAB): [M-Na], 3 bromine isotope pattern, 617,

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619, 621, 622; Anal. Calc. for $C_{24}H_{12}Br_3O_3SNa \cdot 0.75 H_2O$: C, 43.90, H, 2.07, N, 0.00. Found: C, 44.09, H, 2.18, N, 0.03.

Example 81.

5 [(4-Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dicyano-phenoxy]-acetic acid

5-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-hydroxy-isophthalonitrile (0.455 g, 1.21 mmol), methyl bromoacetate (0.351 mL, 3.63 mmol), potassium carbonate (0.251 g, 1.81 mmol) and N,N-dimethylformamide (5.0 mL) were combined and stirred at ambient temperature for two days. The reaction mixture was diluted with
10 water (60 mL) and acidified with 10% aqueous HCl to pH 1 and aqueous was extracted with ethyl acetate (100 mL). The ethyl acetate extract was washed with water, dried with brine and anhydrous $MgSO_4$, and concentrated to provide a white solid. The solid was dissolved in ethyl acetate (60 mL) and silica gel was added. Solvent was removed and the adsorbate was flash chromatographed (eluent 8:2
15 petroleum ether: ethyl acetate) to provide the methyl ester as a white solid (0.370 g, 83%): Aqueous potassium carbonate (170 mg in 5 mL of water, 1.23 mmol) was added to a stirred solution of this methyl ester (0.275 g, 0.613 mmol) in THF (10 mL) at ambient temperature. After 31 h the reaction mixture was diluted with water (100 mL) and acidified with 10% aqueous HCl to pH 1 and aqueous was extracted with
20 ethyl acetate (150 mL). The ethyl acetate extract was washed with water, dried with brine and anhydrous $MgSO_4$, and concentrated to provide the title compound as a white solid (0.207 g, 78%): mp 134-136°C: NMR ($CDCl_3$): δ 8.43 (s, 1H), 7.98 (dd J = 8, 1 Hz, 1H), 7.91 (s, 2H), 7.8 (dd J = 8, 1 Hz, 1H), 7.58 (ddd, J = 8, 7, 1 Hz, 1H), 7.49-7.42 (m, 3H), 7.36 (dd, J = 8, 1 Hz, 1H), 7.18 (ddd, J = 8, 7, 1 Hz, 1H), 6.70 (dd, J = 8, 1 Hz, 1H), 4.47 (s, 2H); MS (EI): 434 (100%, MI); High resolution MS (EI) Calc. for $C_{26}H_{14}N_2O_3S$: High resolution MS (EI) Calc. for $C_{26}H_{14}N_2O_3S$: 434.072516, Found: 434.078475 ; Anal. Calc. for $C_{26}H_{14}N_2O_3S$: C, 71.88, H, 3.25, N, 6.45. Found: C, 70.80, H, 3.14, N, 6.18.

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Example 82.**[(4-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-cyano-phenoxy]-acetic acid**

5-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-hydroxy-benzonitrile (0.386 g, 1.1 mmol), methyl bromoacetate (0.266 mL, 2.75 mmol), potassium carbonate (0.228 g, 1.65 mmol) and N,N-dimethylformamide (5.0 mL) were combined and stirred at ambient temperature for 1.5 h. The reaction mixture was diluted with water (120 mL) and acidified with 10% aqueous HCl to pH 1 and aqueous mixture was extracted with ethyl acetate (150 mL). The ethyl acetate extract was washed with water, dried with brine and anhydrous MgSO₄, and concentrated to provide a white solid. The solid was dissolved in ethyl acetate (60 mL) and silica gel was added. Solvent was removed and the adsorbate was flash chromatographed (eluent 7:3 petroleum ether: ethyl acetate) to provide the methyl ester as a white solid (0.195 g, 42%). Aqueous potassium carbonate (124 mg in 4 mL of water, 0.90 mmol) was added to a stirred solution of this methyl ester (0.190 g, 0.45 mmol) in THF (5 mL) at ambient temperature. After 23 h the reaction mixture was diluted with water (80 mL) and acidified with 10% aqueous HCl to pH 1 and aqueous was extracted with ethyl acetate (100 mL). The ethyl acetate extract was washed with water, dried with brine and anhydrous MgSO₄, and concentrated to provide the title compound as a white solid (0.116 g, 63%): mp 235-236°C: NMR (CDCl₃): δ 8.38 (s, 1H), 7.96 (d J = 8 Hz, 1H), 7.81 (dd, J = 8, 1 Hz, 1H), 7.72 (d, J = 2 Hz, 1H), 7.61 (dd J = 8, 1 Hz, 1H), 7.55 (ddd, J = 8, 7, 1 Hz, 1H), 7.45-7.38 (m, 3H), 7.19 (d, J = 8 Hz, 1H), 7.12 (ddd, J = 8, 7, 1 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 5.04 (s, 2H); MS (EI): 409 (100%, MI); Anal. Calc. for C₂₅H₁₅NO₃S: C, 73.33, H, 3.69, N, 3.42. Found: C, 71.66, H, 3.33, N, 3.31.

Example 83.**(4-Benzo[b]naphtho[2,3-d]thiophen-11-yl-2,6-diiodo-phenoxy)-acetic acid**

4-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diiodo-phenol (0.543 g, 0.94 mmol), methyl bromoacetate (0.181 mL, 1.88 mmol), potassium carbonate (0.141 g, 1.03 mmol) and N,N-dimethylformamide (5.4 mL) were combined and stirred at

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- ambient temperature for 1 h. The reaction mixture was added to water and filtered. The solid was washed with water and dried in vacuo to provide the (4-benzo[b]-naphtho[2,3-d]thiophen-11-yl-2,6-diiodo-phenoxy)-acetic acid methyl ester as a white solid (0.537 g, 88%): mp 203-205 °C. Aqueous potassium hydroxide (0.5 N, 2.54 mL, 1.28 mmol) was added to a stirred solution of this methyl ester (0.55 g, 0.85 mmol) in THF (5.0 mL) at ambient temperature. After 1 h the solution was concentrated, diluted with water (75 mL) and acidified with 10% aqueous HCl. The solid was filtered and washed with water to provide the title compounds as a white solid (0.428 g, 80%): mp 250-252°C: NMR (DMSO-d₆): δ 8.66 (s, 1H), 8.07 (d, J = 8 Hz, 1H), 8.01 (d, J = 8 Hz, 1H), 7.93 (s, 2H), 7.61 (ddd, J = 8, 7, 1 Hz, 1H), 7.54-7.48 (m, 2H), 7.47 (ddd, J = 8, 7, 1 Hz, 1H), 7.27 (ddd, J = 8, 7, 1 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 4.69 (s, 2H); MS (EI): 636 (100%, MI); Anal. Calc. for C₂₄H₁₄I₂O₃S: C, 45.31, H, 2.22, N, 0.00. Found: C, 44.95, H, 1.99, N, 0.23.
- The compounds in Examples 84-95 were prepared using the procedure in Example 83 and the appropriate starting material.

Example 84.

[4-Benzo[b]naphtho[2,3-d]thiophen-11-yl-phenoxy]-acetic acid

- From 4-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol (Example 14). White solid: mp 221-223°C: NMR (DMSO-d₆): δ 13.05 (broad s, 1H), 8.61 (s, 1H), 8.05 (d, J = 8 Hz, 1H), 7.96 (d, J = 7 Hz, 1H), 7.58 (ddd, J = 8, 7, 1 Hz, 1H), 7.51-7.40 (m, 3H), 7.33 (d, J = 9 Hz, 2H), 7.23 (d, J = 9 Hz, 2H), 7.12 (ddd, J = 8, 7, 1 Hz, 1H), 6.71 (ddd, J = 8, 1, 1 Hz, 1H), 4.86 (s, 2H); MS (EI): [M⁺], 384 (100%); Anal. Calc. for C₂₄H₁₆O₃S: C, 74.98, H, 4.20, N, 0.00. Found: C, 74.62, H, 4.14, N, 0.08.

Example 85.

(4-Benzo[b]naphtho[2,3-d]thiophen-11-yl-2-iodo-phenoxy)-acetic acid

- From 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-iodo-phenol (Example 27). White solid: mp 248-249°C: NMR (DMSO-d₆): δ 8.63 (s, 1H), 8.05 (d, J = 8 Hz,

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1H), 7.98 (d, J = 7 Hz, 1H), 7.81 (d, J = 2 Hz, 1H), 7.61-7.56 (m, 1H), 7.49-7.48 (m, 2H), 7.44 (ddd, J = 8, 7, 1 Hz, 1H), 7.41 (dd, J = 8, 2 Hz, 1H), 7.20 (d, J = 8, Hz, 1H), 7.17 (ddd, J = 8, 7, 1 Hz, 1H), 6.75 (d, J = 8, Hz, 1H), 4.96 (s, 2H); MS (EI): 510 (100%, MI); Anal. Calc. for C₂₄H₁₅IO₃S: C, 56.48, H, 2.96, N, 0.00. Found: C, 56.35, H, 2.84, N, 0.27.

Example 86.

{2,6-Dimethyl-4-[6-methyl-(benzo[b]naphtho[2,3-d]thiophen-11-yl)]-phenoxy}-acetic acid

10 From {2,6-dimethyl-4-[6-methyl-(benzo[b]naphtho[2,3-d]thiophen-11-yl)]-phenoxy}-acetic acid methyl ester (Example 25). White solid: mp 155-181°C; NMR (DMSO-d₆); δ 12.95 (broad s, 1H), 8.23 (d, J = 8 Hz 1H), 7.97 (d, J = 8 Hz, 1H), 7.63 (d, J = 8, 7, 1 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 7.47 (ddd, J = 8, 7, 1 Hz, 1H), 7.41 (ddd, J = 8, 8, 1 Hz, 1H), 7.15 (ddd, J = 8, 7, 1 Hz, 1H), 7.05 (s, 2H), 6.67 (d, J = 8
15 Hz, 1H), 4.59 (s, 2H), 2.92 (s, 3H), 2.34 (s, 6H). MS (EI): [M⁺] 426 (100%); Anal. Calc. for C₂₇H₂₂O₃S: C, 76.03, H, 5.20, N, 0.00. Found: C, 75.64, H, 5.31, N, 0.02.

Example 87.

[4-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid

20 From [4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid, methyl ester ester (Example 41). White solid: mp 198-200°C; NMR (CDCl₃); δ 8.34 (ddd, J = 8, 1, 1 Hz, 1H), 7.80 (ddd, J = 8, 1, 1 Hz, 1H), 7.66-7.61 (m, 2H), 7.45-7.38 (m, 2H), 7.36 (d, J = 9 Hz, 2 H), 7.22 (d, J = 9 Hz, 2H), 7.09 (ddd, J = 8, 7, 1 Hz, 1H), 6.71 (ddd, J = 8, 1, 1 Hz, 1H), 4.89 (s, 2H); MS (EI): [M⁺], 1 bromine isotope
25 pattern, 462 (95%), 464 (100%);
Anal. Calc. for C₂₄H₁₅BrO₃S•0.6CH₃CO₂H•0.28H₂O: C, 60.00, H, 3.37, N, 0.00. Found: C, 59.82, H, 3.42, N, 0.03.

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Example 88.**[2,6-Dibromo-4-(6-cyano-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid**

From [2,6-dibromo-4-(6-cyano-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid, methyl ester (Example 58). White solid: mp 259-261°C: NMR (DMSO-d₆); δ 13.2 (broad s, 1H), 8.27 (d, J = 8 Hz, 1H), 8.16 (d, J = 8, 1H), 7.91 (ddd, J = 8, 7, 1 Hz, 1H), 7.89 (s, 2H), 7.74-7.65 (m, 2H), 7.59 (ddd, J = 8, 7, 1 Hz, 1H), 7.38 (ddd, J = 8, 7, 1 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 4.78 (s, 2H); MS (EI): [M⁺], 2 bromine isotope pattern, 565 (45%), 567 (100%) 569 (50%); Anal. Calc. for C₂₅H₁₃Br₂NO₃S: C, 52.93, H, 2.31, N, 2.47. Found: C, 51.96, H, 2.07, N, 2.31.

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Example 89.**[4-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenoxy]-acetic acid**

From 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropylphenol (Example 40). White solid: mp: 220-221°C; NMR (CDCl₃); δ 8.37 (ddd, J = 8, 1, 1, 1H), 7.81 (ddd, J = 8, 1, 1 Hz, 1H), 7.69 (ddd, J = 8, 1, 1 Hz, 1H), 7.66 (ddd, J = 8, 8, 1, 1H), 7.48 (ddd, J = 8, 8, 1 Hz, 1H), 7.38 (ddd, J = 8, 8, 1 Hz, 1H), 7.19 (s, 2H), 7.02 (ddd, J = 8, 8, 1 Hz, 1H), 6.54 (d, J = 8 Hz, 1H), 4.69 (s, 2H), 3.42 (septuplet, J = 7 Hz, 2H), 1.28 (d, J = 7 Hz, 6H), 1.23 (d, J = 7 Hz, 6H); MS (+FAB): 546 (90%), 548 (100); Anal. Calc. for C₃₀H₂₇BrO₃S: C, 65.81, H, 4.97, N, 0.00. Found: C, 65.56, H, 4.89, N, 0.10.

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Example 90.**[3-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid**

From 3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 42). White solid: mp 180-181°C: MS (+FAB): [M⁺], 462; Anal. Calc. for C₂₄H₁₅BrO₃S: C, 62.21, H, 3.26, N, 0.00. Found: C, 61.90, H, 3.19, N, 0.13.

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Example 91.[2-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid

From 2-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 68). White solid: mp 174-175°C: MS (+FAB): [M+], 2 bromine isotope pattern, 540, 542, 544; Anal. Calc. for C₂₄H₁₄Br₂O₃S: C, 53.16, H, 2.60, N, 0.00. Found: C, 52.91, H, 2.75, N, 0.48.

Example 92.

10 [2,4-Dibromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid

From 2,4-dibromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 69). White solid: mp 256-258°C: MS (+FAB): [M+], 618; Anal. Calc. for C₂₄H₁₃Br₃O₃S: C, 46.41, H, 2.11, N, 0.00. Found: C, 46.26, H, 2.17, N, 0.07.

15 **Example 93.**

5-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-carboxymethoxy-phenoxy]-acetic acid

From 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol (Example 42). White solid: mp 222-224°C: MS (+FAB): [M+], 536; Anal. Calc. for C₂₆H₁₇BrO₆S: C, 58.11, H, 3.19, N, 0.00. Found: C, 57.58, H, 3.00, N, 0.15.

Example 94.

3-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-carboxymethoxy-phenoxy]-acetic acid

25 From 3-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol (Example 70). White solid: mp 135-137°C: MS (EI): [M+], 2 bromine isotope pattern, 614, 616, 618; Anal. Calc. for C₂₆H₁₆Br₂O₆S: C, 50.67, H, 2.26, N, 0.00. Found: C, 49.45, H, 2.73, N, 0.11.

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Example 95.**4-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-carboxymethoxy-phenoxy]-acetic acid**

From 4-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-
5 1,2-diol (Example 71). White solid: mp 256-257°C: MS (EI): [M+], 2 bromine
isotope pattern, 614, 616, 618; Anal. Calc. for C₂₆H₁₆Br₂O₆S: C, 50.67, H, 2.26, N,
0.00. Found: C, 50.88, H, 2.96, N, 0.04.

Example 96.**(S)-2-Hydroxy-3-phenylpropionic acid, methyl ester**

A solution of commercially available (S)-2-hydroxy-3-phenylpropionic acid
(5.0 g, 30.1 mmol) and p-toluenesulfonic acid hydrate (1g) in methanol (125 mL)
was refluxed with removal of water using 3A molecular sieves for 17 h. The solution
was concentrated and dissolved in ether. The ether solution was washed with
15 saturated sodium bicarbonate, brine and concentrated to provide the title compound as
a white solid (5.32 g, 98%): NMR (CDCl₃); δ 7.36-7.20 (m, 5H), 4.47 (ddd, J = 5, 6,
7 Hz, 1H), 3.78 (s, 3H), 3.14 (dd, J = 5, 14 Hz, 1H), 2.97 (dd, J = 7, 14 Hz), 2.69 (d, J
= 6Hz, 1H).

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Example 97.**(R)-2-Hydroxy-3-phenylpropionic acid, methyl ester**

Prepared from commercially available (R)-2-hydroxy-3-phenylpropionic acid
according to the procedure in Example 96. White solid: NMR (CDCl₃); δ 7.34-7.20
(m, 5H), 4.47 (ddd, J = 5, 6, 7 Hz, 1H), 3.78 (s, 3H), 3.14 (dd, J = 5, 14 Hz, 1H), 2.97
25 (dd, J = 7, 14 Hz), 2.69 (d, J = 6Hz, 1H).

Example 98.**D,L-Indole-3-lactic acid methyl ester**

Prepared from commercially available D, L-indole-3-lactic acid according to
30 the procedure in Example 96. White solid: mp 42-44 °C: NMR (CDCl₃); δ 8.07 (m,

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1H, NH), 7.61 (d, J = 8 Hz, 1H), 7.34 (d, J = 8 Hz, 1H), 7.19-7.10 (m, 3H), 5.45 (q, J = 6 Hz, 1H), 3.72 (s, 3H), 3.25 (dd, J = 7, 6 Hz, 2H), 2.75 (d, J = 6 Hz, 1H, OH); MS (EI): [M+], 219.

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Example 99.**(S)-(+)- α -Hydroxy-1,3-dioxo-2-isoindolinebutyric acid, methyl ester**

Prepared from commercially available (S)-(+)- α -hydroxy-1,3-dioxo-2-isoindolinebutyric acid according to the procedure in Example 9. White solid: mp 123-124.5°C; MS (EI): [M+], 263; Anal. Calc. for C₁₃H₁₃NO₅: C, 59.31, H, 4.98, N, 5.32. Found: C, 59.04, H, 5.02, N, 5.06.

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Example 100.**L- β -Imidazolelactic acid, methyl ester, hydrochloride**

Thionyl chloride (4.8 mL, 68.4 mmol) was added dropwise to a stirred, ambient temperature suspension of commercially available L- β -imidazolelactic acid, hydrochloride (1.11 g, 5.7 mmol) in methanol (7 mL) under a dry nitrogen atmosphere over a period of 10 min. The solution was heated in an 60°C oil bath for 2 days. Upon cooling to room temperature, the reaction mixture was concentrated, chased with ethyl ether to provide the title compound as a sticky white solid (1.07 g, 90%); NMR (DMSO-d₆): δ 8.63 (s, 1H), 7.23 (s, 1H), 4.35 (t, J = 6 Hz, 1H), 3.62 (s, 3H, OCH₃), 2.90 (d, J = 6 Hz, 2H); MS (EI): 170 (10%, MI), 111(40%), 81(100%).

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Example 101.**N-t-BOC-L- β -Imidazolelactic acid, methyl ester**

Triethylamine (0.878 mL, 6.3 mmol) was added dropwise to a stirred, ambient temperature solution of L- β -imidazolelactic acid, methyl ester, hydrochloride (0.87 g, 4.2 mmol) in methanol (12 mL) under a dry nitrogen atmosphere. The stirring was continued at ambient temperature for 40 min. After 6 h., the reaction mixture was concentrated to yield an oil and dichloromethane (150 mL) was added. The dichloromethane was washed with water and brine. Silica gel (12 mL) was added.

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Solvents were removed and the silica adsorbate was flash chromatographed (eluent 4 : 6 petroleum ether : ethyl acetate) to provide the title compound as an oil (0.86 g, 75%): MS (EI): [M+], 270.

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Example 102.**(S)-2-[4-Nitrobenzoyl]-4-phenylbutyric acid, ethyl ester**

To a cold (ice bath) solution of commercially available (R)-2-hydroxy-4-phenyl-butyrate, ethyl ester (1.86mL, 9.60mmole), p-nitrobenzoic acid (6.42g, 38.4mmole, 4 eq) and triphenylphosphine (10.07g, 38.4 mmole, 4 eq.) in anhydrous tetrahydrofuran (110 mL) was added diethyl azodicarboxylate (6.05 mL, 38.4 mmole, 4 eq) dropwise over a period of 40 minutes keeping the internal temperature between 4 and 5°C. After stirring for one additional hour, the ice bath was removed and the solution was allowed to stir at ambient temperature for 5 days. The solvents were removed and the residue was redissolved in a mixture of ether and ethyl acetate (600 mL). Silica gel (200 mL) was added and the solvents removed. The adsorbate was flash chromatographed (gradient: 80/20 - 70/30 petroleum ether / ethyl acetate) to give the title compound as a yellow oil (4.03g): NMR (CDCl₃); δ 8.30 (d, J = 9 Hz, 2H), 8.18 (d, J = 9 Hz, 2H), 7.38 - 7.18 (m, 5H), 5.28 (t, J = 2Hz, 1H), 4.23 (q, J = 7Hz, 2H), 2.85 (t, J = 8Hz, 2H), 2.40 - 2.33(m, 2H), 1.29 (t, J = 7H, 3H); MS [(+) FAB]: [M +H] m/z = 358.

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Example 103.**(S)-2-Hydroxy-4-phenylbutyric acid, ethyl ester**

To a suspension of potassium cyanide (0.176g, 2.70 mmole) in absolute ethanol (43mL) was added a solution of (S)-2-[4-nitrobenzoyl]-4-phenylbutyrate, ethyl ester (3.86g, 10.8 mmole) in absolute ethanol (38mL) dropwise over a period of 0.5 hours. After stirring 2.25 hours the solvent was removed and the residue was diluted with water and acidified with dilute hydrochloric acid. The organics were extracted with ether. The extracts were combined, silica gel (60 mL) was added and the solvent was removed. The adsorbate was flash chromatographed, eluent (gradient

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90/10 - 80/20 petroleum ether / ethyl acetate) and the solvents were chased with benzene to give the title compound as a yellow oil (1.67g, 74%): $[\alpha]_{25D}^{+178.23}$ (10.98mg/mL CHCl₃); NMR (CDCl₃); δ 7.38 - 7.16 (m, 5H), 4.30 - 4.10 (m, 3H), 2.9 - 2.6 (m, 3H), 2.2 - 1.9 (m, 2H), 1.15 (t, 4Hz, 3H);.

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Example 104.3-Pyridin-3-yl-propionic acid, ethyl ester

According to the procedure of B.A. Lefker, W.A.Hada, P.J. McGarry *Tetrahedron Lett.* **1994**, 35, 5205-5208, a solution of sodium bis(trimethylsilyl)amide (1.0 N in THF, 44.3 mL, 44.3 mmol) was added dropwise at a rate to keep the temperature below -50°C to a stirred solution of 3-pyridine carboxaldehyde (4.41 mL, 46.7 mmol), ethyl chloroacetate (4.93 mL, 46.7 mmol) and THF (34 mL) under a dry nitrogen atmosphere. After 45 min at -78°C, the reaction mixture was warmed to 0°C and then quenched with water and concentrated. The residue was partitioned between ether and water. The ether phase was dried with brine and concentrated. The residue was dissolved in ethyl acetate and palladium hydroxide on carbon (wet, Degussa type, 20% Pd content, 1 g) was added. The mixture was hydrogenated at 45 psi hydrogen pressure for 2 h. The reaction mixture was filtered thru sulka floc and the solvent was removed. The residue was flash chromatographed (2:3 petroleum ether: ethyl acetate, eluent) to provide the title compound as an oil (3.83 g, 42%): NMR (CDCl₃); 8.24 (m, 2H), 7.60 (d, 1H), 7.22 (dd, 1H), 4.45 (t, 1H), 4.22 (q, 2H), 3.15 (dd, 1H), 2.95 (dd, 1H), 1.27 (t, 3H).

Example 105.(S)-(+)- α ,3-Dihydroxy-1-oxo-2-isoindolinebutyric acid, methyl ester

Sodium borohydride (0.474 g, 12.54 mmol) was added portionwise to a -20 °C, stirred solution of (s)-(+)- α -hydroxy-1,3-dioxo-2-isoindolinebutyric acid methyl ester (3.0 g, 11.4 mmol) in THF/water (30/1.38 mL) for 6 hours. Upon cooling to room temperature, the reaction mixture was carefully quenched and acidified with 10% aqueous HCl. Aqueous mixture was extracted with ethyl acetate (300 mL). The

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ethyl acetate extract was washed with water and brine. Silica gel (15 mL) was added. Solvents were removed and the silica adsorbate was flash chromatographed (eluent 95 : 5 petroleum ether: dichloromethane) to provide the title compound as an oil (0.96 g, 32%): MS (EI): [M+], 265.

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Example 106.(s)-(+)- α -Hydroxy-1-oxo-2-isoindolinebutyric acid, methyl ester

Trifluoroacetic anhydride (1.1 mL, 7.66 mmol) was added dropwise to a stirred suspension of (s)-(+)- α ,3-dihydroxy-1-oxo-2-isoindolinebutyric acid, methyl ester (0.84 g, 3.19 mmol) in chloroform (10 mL) under a dry N₂ atmosphere for 2 hours. After the reaction mixture was concentrated to yield an oil, trifluoroacetic acid (3.4 mL) and triethylsilane (1.1 mL, 3.83 mmol) were added at ambient temperature under a dry nitrogen atmosphere. After 6 hours, the reaction mixture was carefully quenched with 10% aqueous sodium bicarbonate. Aqueous mixture was extracted with dichloromethane (150 mL). The dichloromethane extract was washed with water and brine. Silica gel (12 mL) was added. Solvents were removed and the silica adsorbate was flash chromatographed (eluent 15 : 85 petroleum ether : ethyl acetate) to provide an oil (0.50 g, 63%): mp 73.5-74.5°C: MS (EI): [M+], 247.

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Example 107.(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester

Diethylazodicarboxylate (0.437 mL, 2.74 mmol) was added dropwise to a stirred, room temperature suspension of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho- [2,3-d]thiophen-11-yl)-phenol (1.00 g, 1.83 mmol), (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (0.494 g, 2.74 mmol), triphenylphosphine (0.72 g, 2.74 mmol) and benzene (12 mL) under a dry nitrogen atmosphere. Dissolution occurred and the solution was heated in an 80°C oil bath for 3.5 h. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane and silica gel (30 mL) was added. The reaction mixture was concentrated and the silica adsorbate was flash

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chromatographed (96 : 4 petroleum ether : ethyl acetate) to provide the title compound as a white solid (1.20 g, 90%): mp 138-139.5°C: NMR (CDCl₃); δ 8.36 (ddd, J = 8, 1, 1 Hz, 1H), 7.83 (ddd, J = 8, 1, 1 Hz, 1H), 7.68 (ddd, J = 8, 7, 1 Hz, 1H), 7.60 (dd, J = 5, 2 Hz, 2H), 7.60-7.48 (m, 2H), 7.46-7.28 (m, 6H), 7.18 (ddd, J = 8, 7, 1 Hz, 1H), 6.74 (ddd, J = 8, 1, 1 Hz, 1H), 5.26 (t, J = 8 Hz, 1H), 3.76 (s, 3H), 3.59 (dd, J = 8, 5 Hz, 2H); MS (FAB+): [M⁺], 3 bromine isotope pattern, 722 (30%), 724 (70%) 726 (100%) 728 (35%); Anal. Calc. for C₃₂H₂₁Br₃O₃S: C, 52.99, H, 2.99, N, 0.00. Found: C, 52.60, H, 2.68, N, 0.07.

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Example 108.

(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Aqueous potassium hydroxide (1 N, 6.37 mL, 6.37 mmol) was added to a stirred solution of (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester (2.31 g, 3.19 mmol) in THF (22 mL)/methanol (15 mL). After 2h the solution was concentrated, diluted with water (100 mL) and acidified with 10% aqueous HCl. The solid was filtered, washed with water and triturated with petroleum ether. It was then recrystallized from methanol to provide the title compound as a white solid (1.52 g, 67%): mp 140-142°C: [α]_D²⁵ = +25.66 (10.52 mg/mL CHCl₃); NMR (DMSO-d₆); δ 13.26 (broad s, 1H), 8.29 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.80 (m, 1H), 7.79 (dd, J = 7, 3 Hz, 2H), 7.63 (ddd, J = 8, 7, 1 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 7.51 (ddd, J = 8, 7, 1 Hz, 1H), 7.41 (d, J = 7 Hz, 2H), 7.38-7.32 (m, 3H), 7.31-7.22 (m, 3H), 6.64 (d, J = 8 Hz, 1H), 5.32 (t, J = 7 Hz, 1H), 3.41 (d, J = 7 Hz, 2H); MS (EI): [M⁺], 3 bromine isotope pattern, 708 (35%), 710 (90%) 712 (100%) 714 (40%); Anal. Calc. for C₃₁H₁₉Br₃O₃S: C, 52.35, H, 2.69, N, 0.00. Found: C, 52.46, H, 2.59, N, 0.10. Chiral analytical HPLC determined that this compound had approx. 100% EE [column: Chirobiotic V, 5 micron (4.6 x 250 mm); isocratic, 1:1 ethanol: hexane; flow rate = 0.80 mL/min; injection volume = 0.3 μL; sample conc. = 0.25 mg/mL; retention time, R-enantiomer = 21 min; retention time, S-enantiomer = 16 min.].

Example 109.

(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, sodium salt

- 5 Sodium hydroxide (1 N, 0.417 mL, 0.417 mmol) was added to a stirred room temperature solution of (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]-thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid (0.297 g, 0.418 mmol) in THF (1.3 mL)/methanol (1.3). After 30 min, the solvent was removed and the solvent was repeatedly chased with benzene via rotoevaporation and dried overnight at 70°C to
- 10 provide the title compound as a white solid (0.31 g, 100%): mp 261-265°C: NMR (DMSO-d₆); δ 8.27 (d, J = 8 Hz, 1H), 8.03 (d, J = 8 Hz, 1H), 7.79 (ddd, J = 8, 8, 1 Hz, 1H), 7.63 (ddd, J = 8, 7, 1 Hz, 1H), 7.58-7.47 (m, 4H), 7.41 (d, J = 7 Hz, 2H), 7.35-7.32 (m, 1H), 7.22 (t, J = 7 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 5.42 (dd, J = 8, 4 Hz, 1H), 3.4 (m, 2H); MS (ESI): [M-H]⁻, 3 bromine isotope pattern, 707, 709, 711,
- 15 713; Anal. Calc. for C₃₁H₁₈Br₃O₃SNa: C, 50.78, H, 2.47, N, 0.00. Found: C, 50.82, H, 2.79, N, 0.02.

Example 110.

(S)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester

- 20 Diethylazodicarboxylate (0.839 mL, 5.50 mmol) was added dropwise to a stirred, room temperature suspension of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (2.00 g, 3.55 mmol), (R)-2-hydroxy-3-phenylpropionic acid, methyl ester (0.96 g, 5.50 mmol), triphenylphosphine (1.40 g, 5.50 mmol) and
- 25 benzene (15 mL) under a dry nitrogen atmosphere. Dissolution occurred and the solution was heated in an 80°C oil bath for 19 h. Upon cooling to room temperature, the reaction mixture was diluted with ether and silica gel (60 mL) was added. The reaction mixture was concentrated and the silica adsorbate was flash chromatographed (95:5 petroleum ether : ethyl acetate) to provide the title compound
- 30 as a white solid (2.48 g, 94 %): mp 140-143°C: [a]_D²⁵ = -56.87° (10.02 mg/mL

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CHCl₃); NMR (CDCl₃); δ 8.36 (ddd, J = 8, 1, 1 Hz, 1H), 7.83 (ddd, J = 8, 1, 1 Hz, 1H), 7.68 (ddd, J = 8, 7, 1 Hz, 1H), 7.60 (dd, J = 5, 2 Hz, 2H), 7.60-7.49 (m, 2H), 7.46-7.27 (m, 6H), 7.18 (ddd, J = 8, 7, 1 Hz, 1H), 6.74 (ddd, J = 8, 1, 1 Hz, 1H), 5.26 (dd, J = 8, 6 Hz, 1H), 3.76 (s, 3H), 3.59 (dd, J = 8, 5 Hz, 2H); MS (FAB+): [M+], 3
5 bromine isotope pattern, 722 (31%), 724 (94%) 726 (100%) 728 (40%); Anal. Calc. for C₃₂H₂₁Br₃O₃S: C, 52.99, H, 2.99, N, 0.00. Found: C, 52.99, H, 2.85, N, 0.03.

Example 111.

10 (S)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Aqueous potassium hydroxide (1 N, 2.40 mL, 2.40 mmol) was added to a stirred solution of (S)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester (0.88 g, 1.21 mmol) in THF (12 mL)/methanol (8 mL). After 2h the solution was concentrated, diluted with water
15 (50 mL) and acidified with 10% aqueous HCl. The reaction mixture was then partitioned between water and ether. The ether phase was concentrated and triturated with ether and pet. ether. It was then recrystallized from methanol to provide the title compound as a white solid (0.54 g, 63%): [a]_D²⁵ = -24.81° (10.08 mg/mL CHCl₃); NMR (CDCl₃); δ 8.36 (d, J = 8 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 7.68 (ddd, J = 8, 5, 3
20 Hz, 1H), 7.58 (dd, J = 10, 2 Hz, 2H), 7.54-7.48 (m, 2H), 7.44-7.27 (m, 6H), 7.16 (ddd, J = 8, 7, 1), 6.72 (d, J = 8 Hz, 1H), 5.45 (t, J = 7 Hz, 1H), 3.59 (d, J = 7 Hz, 2H); MS (EI): [M+], 3 bromine isotope pattern, 708 (24%), 710 (80%) 712 (100%) 714 (40%); Anal. Calc. for C₃₁H₁₉Br₃O₃S: C, 52.35, H, 2.69, N, 0.00. Found: C, 52.05, H, 2.59, N, 0.10. Chiral analytical HPLC determined that this compound had approx. 100%
25 EE [column:Chirobiotic V, 5 micron (4.6 x 250 mm); isocratic, 1:1 ethanol: hexane; flow rate = 0.80 mL/min; injection volume = 0.3 μ L; sample conc. = 0.25 mg/mL; retention time, R-enantiomer = 21 min; retention time, S-enantiomer = 16 min.]

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Example 112.

(R)-2-[2,6-Dibromo-4-(6-methoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester

Prepared from 2,6-dibromo-4-(6-methoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 63) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96) according to the procedure of Example 107. White solid (0.608 g, 96%): NMR (THF-d8); δ 8.29-8.26 (m, 1H), 7.87 (d., J = 8 Hz, 1H), 7.72 - 7.68 (dd, 2H, J = 4, 2 Hz), 7.60 - 7.56 (m, 2H), 7.48-7.37 (m, 4H), 7.32 - 7.28 (m, 2H), 7.25-7.23 (m, 2H), 7.20 - 7.15 (m, 2H), 6.85 - 6.82 (m, 1H), 5.22(dd, 1H, J = 14, 2, Hz), 4.17 (s, 1H), 3.71 (s, 1H), 3.58(s, 6H), ; MS (FAB+): [M+], 2 bromine isotope pattern, 674 (40%), 676 (66%), 678 (45%); Anal. Calc. for C₃₃H₂₄Br₂O₄S: C, 58.60, H, 3.58, N, 0.00. Found: C, 58.11, H, 3.53, N, 0.19.

Example 113.

(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-butyric acid

Diethylazodicarboxylate (DEAD, 0.210 mL, 1.33 mmol) was added to a stirred, room temperature solution of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (0.500 g, 0.888 mmol), (S)-2-hydroxy-4-phenyl-butyrate, ethyl ester (0.277 g, 1.33 mmol), triphenylphosphine (0.350 g, 1.33 mmol) and benzene (3.8 mL) under a dry nitrogen atmosphere. Dissolution occurred and the solution was heated in an 80°C oil bath for 2 h. Upon cooling to room temperature, the reaction mixture was diluted with ether and silica gel was added. The reaction mixture was concentrated and the silica adsorbate was flash chromatographed (95 : 5 petroleum ether : ethyl acetate) to provide a white solid (0.570 g, 85%). Aqueous potassium hydroxide (1 N, 1.4 mL, 1.4 mmol) was added to a stirred solution of this solid (0.562 g, 0.746 mmol) in THF (12 mL)/methanol (5 mL). After 3h the solution was concentrated, diluted with water and acidified with 10% aqueous HCl. The solid was filtered, washed with water and triturated with petroleum ether to provide the title compound as a white solid (0.526 g, 97%): mp 115-120°C: NMR (DMSO-d₆); δ 13.3

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(broad s, 1H), 8.29 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.83 (d, J = 2 Hz, 1H), 7.81 (d, J = 2 Hz, 1H), 7.80 (ddd, J = 8, 7, 1 Hz, 1H), 7.65-7.58 (m, 2H), 7.51 (ddd, J = 8, 8, 1 Hz, 1H), 7.33-7.20 (m, 6H), 6.67 (d, J = 8 Hz, 1H), 5.15 (dd, J = 6 Hz, 1H), 3.00 (m, 1H), 2.79 (m, 1H), 2.34 (m, 2H); MS (FAB+): [M+], 3 bromine isotope pattern, 722, 724, 726, 728; Anal. Calc. for C₃₂H₂₁Br₃O₃S: C, 52.99, H, 2.92, N, 0.00. Found: C, 52.49, H, 2.69, N, 0.17.

The compounds in Examples 114-144 were prepared using the procedure in Example 113 and the appropriate starting materials.

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Example 114.

(S)-2-[4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Prepared from 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 41) and (R)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 97). White solid: [α]_D²⁵ = +17.94° (10.30 mg/mL CHCl₃): NMR (CDCl₃): δ 8.31 (ddd, J = 8, 1, 1 Hz, 1H), 7.76 (ddd, J = 8, 1, 1 Hz, 1H), 7.60 (ddd, J = 8, 8, 1 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.44-7.29 (m, 6H), 7.24-7.20 (m, 4H), 7.19-7.04 (m, 3H), 6.62 (d, J = 8 Hz, 1H), 5.08 (dd, J = 7, 5 Hz, 1H), 3.44 (d, J = 5 Hz, 1H), 3.43 (d, J = 7 Hz, 1H); MS (FAB+): [M+H], bromine isotope pattern, 553 (11%), 569 (12%); Anal. Calc. for C₃₁H₂₁BrO₃S: C, 67.27, H, 3.82, N, 0.00. Found: C, 65.17, H, 3.64, N, 0.04. Analytical HPLC determined that this compound was 98.9% pure [column: novapak, 5 micron (4.6 x 250 mm); isocratic, 7:3 acetonitrile: 0.01 M potassium dihydrogen phosphate, pH = 3.5; flow rate = 1.0 mL/min].

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Example 115.

(S)-2-[2,6-Dibromo-4-(6-cyano-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Prepared from 11-(3,5-dibromo-4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]-thiophene-6-carbonitrile (Example 58) and (R)-2-hydroxy-3-phenylpropionic acid,

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methyl ester (Example 97). White solid: mp 176-178°C: NMR (CDCl₃); δ 8.36 (ddd, J = 8, 1, 1 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.77 (ddd, J = 8, 8, 2 Hz, 1H), 7.58 (d, J = 2 Hz, 1H), 7.61-7.54 (m, 2H), 7.56 (d, J = 2 Hz, 1H), 7.47 (ddd, J = 8, 8, 1 Hz, 1H), 7.41 (ddd, J = 8, 1, 1, 2H), 7.36-7.26 (m, 3H), 7.20 (ddd, J = 8, 8, 1, 1H), 6.75 (ddd, J = 8, 1, 1 Hz, 1H), 5.46 (t, J = 7 Hz, 1H), 3.59 (d, J = 7 Hz, 2H); MS (-FAB): [M-H]⁻, 2 bromine isotope pattern, 654 (2%), 656 (4%), 658 (2%); Anal. Calc. for C₃₂H₁₉Br₂NO₃S: C, 58.47, H, 2.91, N, 2.13 Found: C, 58.23, H, 2.69, N, 2.03.

Example 116.

10 (R)-2-[4-(6-Cyano-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Prepared from 11-(4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene-6-carbonitrile (Example 44) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: mp 145-148°C: [a]_D²⁵ = -2.03° (7.883 mg/mL CHCl₃); NMR (CDCl₃); δ 8.31 (ddd, J = 8, 1, 1 Hz, 1H), 7.78 (ddd., J = 8, 1, 1 Hz, 1H), 7.70 (ddd, J = 8, 8, 1 Hz, 1H), 7.56 (ddd, J = 8, 1, 1 Hz, 1H), 7.47-7.37 (m, 6H), 7.32 (ddd, J = 8, 7, 1 Hz, 1H), 7.20 (dd., J = 8, 2 Hz, 1H), 7.14-7.05 (m, 4H), 6.62 (ddd, J = 8, 1, 1 Hz, 1H), 5.06 (dd, J = 7, 5 Hz, 1H), 3.44 (d, J = 5 Hz, 1H), 3.42 (d, J = 7 Hz, 1H); MS (EI): [M⁺], 499 (100%); Anal. Calc. for C₃₂H₂₁NO₃S: C, 76.93, H, 4.24, N, 2.80. Found: C, 75.77, H, 4.22, N, 2.70.

Example 117.

(R)-2-[4-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Prepared from 4-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol (Example 14) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: [a]_D²⁵ = -19.09° (8.538 mg/mL, CHCl₃); NMR (CDCl₃); δ 8.30 (s, 1H), 7.91 (d, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.55-7.24 (m, 10H), 7.14-7.09 (m, 2H), 7.05 (ddd, J = 8, 7, 1 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 5.09 (dd, J = 8, 5 Hz, 1H), 3.42 (m, 2H); MS (EI): [M⁺] 474 (100%); Anal. Calc. for C₃₁H₂₂O₃S: C, 78.46, H, 4.67, N, 0.00. Found: C, 77.09, H, 4.60, N, 0.03 Analytical HPLC purity (98.5%).

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Example 118.**(S)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-butyric acid**

Prepared from of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 21) and commercially available (R)-2-hydroxy-4-phenyl-butyrate, ethyl ester. White solid: mp 180-181°C: [α]_D²⁵ = +5.83° (10.3 mg/mL CHCl₃); NMR (CDCl₃); δ 8.36 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.67 (ddd, J = 8, 7, 1 Hz, 1H), 7.64 (dd, J = 5, 2 Hz, 2H), 7.63-7.49 (m, 2H), 7.42 (ddd, J = 8, 7, 1 Hz, 1H), 7.34-7.22 (m, 5H), 7.12 (ddd, J = 8, 7, 1 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 5.30 (t, 1H), 3.21-2.87 (m, 2H), 2.59-2.49 (m, 2H); MS (FAB-): [M-H]⁻, 3 bromine isotope pattern, 721, 723, 725, 727; Anal. Calc. for C₃₂H₂₁Br₃O₃S: C, 53.00, H, 2.92, N, 0.00. Found: C, 52.63, H, 2.68, N, 0.09.

Example 119.**(R)-2-[4-(3-Carboxymethoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid**

Prepared from of [11-(4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-yloxy]-acetic acid methyl ester (Example 72) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: mp: 191-201°C: NMR (DMSO-d₆); δ 13.1 (broad s, 2H), 8.45 (s, 1H), 8.01 (d, J = 8 Hz, 1H), 7.55-7.25 (m, 11H), 7.16 (d, J = 9 Hz, 2H), 6.67 (dd, J = 9, 2 Hz, 1H), 6.49 (d, J = 9 Hz, 1H), 5.18 (dd, J = 7, 4 Hz, 1H), 4.74 (s, 2H), 3.28 (dd, J = 7, 4 Hz, 1H), 3.21 (dd, J = 14, 7 Hz, 1H); MS (EI): 458 (80%, M⁺); Anal. Calc. for C₃₃H₂₄O₆S: C, 72.25, H, 4.41, N, 0.00. Found: C, 69.57, H, 4.15, N, 0.32; Analytical HPLC :92% purity.

Example 120.**(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(1H-imidazol-4-yl)-propionic acid, hydrochloride**

Prepared from of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 21) and N-t-BOC-L-β -imidazolelactic acid, methyl ester

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(Example 101). White solid: mp >265°C (dec): NMR (CDCl₃); δ 9.00 (s, 1H), 8.29 (d, J = 8 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 7.84-7.78 (m, 3H), 7.65-7.51 (m, 4H), 7.28 (dd, J = 8, 1 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 5.40 (t, J = 7 Hz, 1H), 3.49-3.47 (m, 2H); MS (+FAB): [M+H]⁺, 3 bromine isotope pattern, 699, 701, 703, 705; Anal. Calc. for C₂₈H₁₇Br₃N₂O₃S: C, 45.59, H, 2.46, N, 3.80. Found: C, 45.69, H, 2.38, N, 3.76.

Example 121.

(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid

10 Prepared from of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 21) and commercially available (S)-lactic acid, methyl ester. White solid: mp 131-133 °C: NMR (CDCl₃); δ 8.37 (d, J = 9 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.71-7.65 (m, 3H), 7.57-7.50 (m, 2H), 7.45 (ddd, J = 8, 7, 1 Hz, 1H), 7.18 (ddd, J = 8, 7, 1 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 5.36 (q, J = 7 Hz, 1H), 1.82 (d, J = 7 Hz, 3H); MS (EI): [M-H]⁺, 3 bromine isotope pattern, 631 (14%), 633 (44 %), 635 (42%), 637 (16%); Anal. Calc. for C₂₅H₁₅Br₃O₃S: C, 47.27, H, 2.38, N, 0.00. Found: C, 47.57, H, 2.33, N, 0.03.

Example 122.

(R,S)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(1H-indol-3-yl)-propionic acid

20 Prepared from of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 21) and D,L-indole-3-lactic acid methyl ester (Example 98). White solid: mp 146-147 °C: NMR (CDCl₃); δ 8.36 (d, J = 9 Hz, 1H), 8.04-8.03 (m, 1H, NH), 7.81 (d, J = 8 Hz, 1H), 7.72-7.65 (m, 2H), 7.60 (s, 2H), 7.59-7.59 (m, 2H), 7.42-7.37 (m, 2H), 7.28 (d, 2 Hz, 1H), 7.22 (ddd, J = 8, 7, 1 Hz, 1H), 7.16 (dd, J = 8, 1 Hz, 1H), 7.12 (dd, J = 8, 1 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 5.45 (t, J = 6 Hz, 1H), 3.75 (d, J = 7 Hz, 2H); MS (FAB⁺): [M+], 3 bromine isotope pattern, 747, 749, 751, 753; Anal. Calc. for C₃₃H₂₀Br₃NO₃S: C, 52.83, H, 2.69, N, 1.87. Found: C, 53.08, H, 2.73, N, 1.19.

Example 123.**2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-hexanoic acid**

Prepared from of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 21) and commercially available (R,S)-2-hydroxypentanoic, methyl ester. White solid: mp 212-213°C: NMR (CDCl₃); δ 8.36 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.67 (ddd, J = 8, 5, 1 Hz, 1H), 7.63 (dd, J = 2, 1 Hz, 2H), 7.58-7.42 (m, 3H), 7.16 (t, J = 8, 1H), 6.75 (d, J = 8 Hz, 1H), 5.23 (t, J = 5 Hz, 1H), 2.26 - 2.16 (m, 2H), 1.8 - 1.73 (m, 1H), 1.60 - 1.41 (m, 3H), 0.99 (t, 3H); MS (EI): [M⁺], 3 bromine isotope pattern, 674 (35%), 676 (90%) 678 (100%) 680 (35%); Anal. Calc. for C₂₈H₂₁Br₃O₃S: C, 49.66, H, 3.12, N, 0.00. Found: C, 49.28, H, 2.90, N, 0.09.

Example 124.**(2R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1-oxo-1,3-dihydro-isoindol-2-yl)-butyric acid**

Prepared from of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 21) and (S)-(+)- α -hydroxy-1-oxo-2-isoindolinebutyric acid methyl ester (Example 106). White solid: mp 239-241°C: NMR (CDCl₃); δ 8.34 (d, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 1H), 7.66 (ddd, J = 8, 7, 1 Hz, 1H), 7.62-7.58 (m, 4H), 7.52-7.47 (m, 3H), 7.39 (ddd, J = 8, 7, 1 Hz, 1H), 7.14 (ddd, J = 8, 7, 1 Hz, 1H), 6.72 (d, J = 8 Hz, 1H), 5.39 (t, J = 7 Hz, 1H), 4.59 (m, 2H), 4.22-3.93 (m, 2H), 2.65 (t, J = 6 Hz, 2H); MS (+FAB): [M+H]⁺, 3 bromine isotope pattern, 778, 780, 782, 784); Anal. Calc. for C₃₄H₂₂Br₃NO₄S: C, 52.33, H, 2.84, N, 1.79. Found: C, 52.11, H, 2.73, N, 1.79.

Example 125.**(R)-2-[2,6-Dibromo-4-(6-trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid**

Prepared from of 2,6-dibromo-4-(6-trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 61) and (S)-2-hydroxy-3-phenylpropionic acid,

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methyl ester (Example 96). White solid: mp 109-143°C; [a]_D²⁵=+47.99° (10.002 mg/mL CH₃OH); NMR (DMSO-d₆); δ 13.26 (s, 1H), 8.30 - 8.27 (m, 1H), 8.06 (d, J = 7 Hz, 1H), 7.87 - 7.81 (m, 3H), 7.71 - 7.60 (m, 2H), 7.52 (dd, J = 8, 1 Hz, 1H), 7.43 - 7.24 (m, 6H), 6.60 (d, J = 8 Hz, 1H), 5.33 (t, J = 7 Hz, 1H), 3.41 (d, J = 7 Hz, 2H); MS (EI): [M⁺], 2 bromine isotope pattern, 698 (8%), 700 (20%) 702 (15%); Anal. Calc. for C₃₂H₁₉Br₂F₃O₃S: C, 54.88, H, 2.74, N, 0.00. Found: C, 55.29, H, 3.11, N, 0.10.

Example 126.

10 (R)-2-[2,6-Dibromo-4-(6-methoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Prepared from of 2,6-dibromo-4-(6-methoxybenzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 63) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: mp 102-110°C: NMR (DMSO-d₆); δ 13.2 (broad peak, 1H), 8.23 (d, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 7.74 (dd, J = 6, 2 Hz, 2H), 7.56 (ddd, J = 8, 7, 1, 1H), 7.56 (ddd, J = 8, 7, 1 1H), 7.51-7.45 (m, 2H), 7.42-7.40 (m, 2H), 7.36 - 7.32 (m, 4H), 7.30 - 7.20 (m, 2H), 6.68 (d, J = 8Hz, 1H), 5.30(t, J = 7Hz, 1H), 4.13(s, 3H), 3.41 (d, J = 7 Hz, 2H); MS (EI): [M⁺], M/z 660 (46%), 662 (100%), 664 (54%); Hi Res MS, Calc. Sample Mass for C₃₂H₂₂Br₂O₄S: 659.960553, Measured Mass: 659.953875, Mass deviation 6.7 nm; Anal. Calc. for C₃₂H₂₂Br₂O₄S·0.23C₆H₆: C, 58.08, H, 3.37 N, 0.00. Found: C, 59.34, H, 3.24, N, 0.04.

Example 127.

25 (R)-2-[2,6-Dibromo-4-(6-chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Prepared from of 2,6-dibromo-4-(6-chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 60) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: [a]_D²⁵/D = +19.63° (8.805 mg/mL, CHCl₃); NMR (DMSO-d₆); δ 13.25-13.22 (broad singlet, 1H), 8.32 (d, J = 8 Hz, 1H), 8.70 (d, J = 8

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Hz, 1H), 7.81-7.79 (ddd, J = 8, 7, 1 Hz, 1H), 7.79 (dd, J = 10, 2 Hz, 2H), 7.64 (ddd, J = 8, 7, 1 Hz, 1H), 7.58-7.49 (m, 2H), 7.42-7.32 (m, 4H,), 7.29-7.24 (m, 2H), 6.66 (d, J = 8 Hz, 1H), 5.32 (t, J = 6 Hz, 1H,), 3.41 (d, J = 7 Hz, 2H); MS (-ESI): [(M-H)+], 2 bromine, 1 chlorine isotope pattern, 663 (40%), 665 (100%), 667 (60%), 669 (17%);
 5 Anal. Calc. for C₃₁H₁₉Br₂ClO₃S: C, 55.84, H, 2.87, N, 0.00. Found: C, 56.95; H, 3.00, N, 0.24.

Example 128.

(R)-2-[2,6-Dibromo-4-(6-phenylsulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-
 10 phenoxy]-3-phenyl-propionic acid

Prepared from of 2,6-dibromo-4-(6-phenylsulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 64) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: NMR (DMSO-d₆); δ 8.50 (d, J = 8 Hz, 1H), 7.98 (d, J = 8 Hz, 1H), 7.83 (d, J = 2 Hz, 1H), 7.81 (d, J = 2 Hz, 1H), 7.71 (ddd, J = 6, 5, 2 Hz, 2H), 7.58 (m, 2H), 7.47 (ddd, J = 8, 8, 1 Hz, 1H), 7.42 (d, J = 8 Hz, 2H), 7.34
 15 (t, J = 7 Hz, 2H), 7.29-7.20 (m, 4H), 7.17-7.08 (m, 3H), 6.67 (d, J = 8 Hz, 1H), 5.35 (t, J = 7 Hz, 1H, CH), 3.41 (d, J = 7 Hz, 2H); MS (+FAB): [M+], 2 bromine isotope pattern, 738 (35%), 740 (90%) 742 (60%); Anal. Calc. for C₃₇H₂₄Br₂O₃S₂: C, 60.01, H, 3.27, N, 0.00. Found: C, 58.57, H, 3.04, N, 0.22.

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Example 129.

(R)-2-[2,6-Dibromo-4-(6-phenylsulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-
phenoxy]-propionic acid

Prepared from of 2,6-dibromo-4-(6-phenylsulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 64) and commercially available (S)-lactic acid, methyl ester. White solid: mp 232-234°C: NMR (DMSO-d₆); δ 8.51 (d, J = 8 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 7.89 (d, J = 2 Hz, 1H), 7.89 (d, J = 2 Hz, 1H), 7.71 (ddd, J = 8, 7, 1 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.60 (ddd, J = 8, 7, 1 Hz, 1H), 7.49 (ddd, J = 8, 7, 1 Hz, 1H), 7.28-7. (m, 4H), 7.17-7.09 (m, 4H), 6.68 (d, J = 8 Hz, 1H), 5.13 (dd, J
 25 = 7, 14 Hz, 1H), 1.64 (d, J = 7 Hz, 2H); MS (+FAB): [M+], 2 bromine isotope
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pattern, 662 (35%), 664 (100%), 666 (60%); Anal. Calc. for C₃₁H₂₀Br₂O₃S₂: C, 56.04, H, 3.03, N, 0.00. Found: C, 55.53, H, 2.86, N, 0.24.

Example 130.

5 (R)-2-[2,6-Dichloro-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Prepared from of 2,6-dichloro-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 67) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: NMR (DMSO-d₆); δ 13.25 (broad s, 1H), 8.29 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.80 (ddd, J = 8, 8, 1, 1H), 7.65-7.61 (m, 1H) 7.63 (d, J = 2 Hz, 1H), 7.61 (d, J = 2 Hz, 1H), 7.55 (dd, J = 8, 1, 1H), 7.51 (dd, J = 8, 1, 1H), 7.41 (dd, J = 8, 1, 2H), 7.34 (ddd, J = 8, 8, 1, 2H), 7.27 (ddd, J = 8, 8, 1, 2H), 6.66 (d, J = 8 Hz, 1H), 5.28 (t, J = 7 Hz, 1H), 3.44-3.30 (m, 2H); MS (+FAB): [M⁺], 1 bromine, 2 chlorine isotope pattern, 620, 622, 624; Anal. Calc. for
15 C₃₁H₁₉BrCl₂O₃S: C, 59.83, H, 3.08, N, 0.00. Found: C, 59.31, H, 2.93, N, 0.40.

Example 131.

(R)-Benzo[b]naphtho[2,3-d]thiophen-11-yl-2,6-diiodo-phenoxy)-3-phenyl-propionic acid

20 Prepared from of 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diiodo-phenol (Example 26) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: mp 115-117°C: NMR (CDCl₃); δ 8.36 (s, 1H), 7.95 (dd J = 8, 1 Hz, 1H), 7.87 (d, J = 2 Hz, 1H), 7.85 (d, J = 2 Hz, 1H), 7.78 (dd, J = 8, 1 Hz, 1H), 7.58-7.27 (m, 9 H), 7.12 (ddd, J = 8, 7, 1 Hz, 1H), 6.77 (d, J = 8, 1 Hz, 1H), 5.56 (t, J = 7
25 Hz, 1H), 3.67-3.55 (m, 2H); MS (EI): [M⁺], 726; Anal. Calc. for C₃₁H₂₀I₂O₃S: C, 51.26, H, 2.77, N, 0.00. Found: C, 51.49, H, 2.87, N, 0.13.

Example 132.

(R)-2-(4-Benzo[b]naphtho[2,3-d]thiophen-11-yl-2,6-diiodo-phenoxy)-propionic acid

30 Prepared from of 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diiodo-phenol (Example 26) and commercially available (S)-lactic acid, methyl ester. White solid:

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mp 134-136: NMR (CDCl₃): δ 8.38 (s, 1H), 7.95 (dd J = 8, 6 Hz, 1H), 7.93 (d, J = 1 Hz, 2H), 7.81 (d, J = 8 Hz, 1H), 7.58 (ddd, J = 8, 7, 1 Hz, 1H), 7.59-7.54 (m, 2H), 7.49-7.40 (m, 2H), 7.15(ddd, J = 8, 7, 1 Hz, 1H), 6.77 (d, J = 8, 1 Hz, 1H), 5.48 (q, J = 7 Hz, 1H), 1.82 (d, J = 7 Hz, 2H); MS (+FAB): [M+H]⁺, 651; Anal. Calc. for C₂₆H₁₆I₂O₃S: C, 46.18, H, 2.48, N, 0.00. Found: C, 46.60, H, 2.50, N, 0.21.

Example 133.

(R)-2-{2,6-Dibromo-4-[6-(2-dimethylamino-ethylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenoxy}-3-phenyl-propionic acid

10 Prepared from of 2,6-dibromo-4-[6-(2-dimethylamino-ethylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol (Example 66) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: mp 169-174°C; NMR (DMSO-d₆): δ 13.3 (broad s, 1H), 8.64 (d, J = 8 Hz, 1H), 8.04 (d, J = 8 Hz, 1H), 7.81 (ddd, J = 8, 7, 1 Hz, 1H), 7.76 (dd, J = 16, 1 Hz), 7.72-7.48 (m, 4H), 7.42-7.22 (m, 7H),
15 6.64 (d, J = 8 Hz, 1H), 5.32 (t, J=7Hz, 1H), 3.36-3.14 (m, 6H); 2.64 (s, 6H); MS (+FAB): [(M+H)⁺], 2 bromine isotope pattern, 734 (55%), 736 (100%), 738 (70%). Anal. calc. for C₃₅H₂₉Br₂NO₃S₂; C, 54.45, H, 3.92, N, 1.81. Found: C, 54.46, H, 3.76, N, 1.66.

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Example 134.

(R)-2-{2,6-Dibromo-4-[6-(pyridin-4-ylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenoxy}-3-phenyl-propionic acid

Prepared from of 2,6-dibromo-4-[6-(pyridin-4-ylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol (Example 65) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: NMR (DMSO- d₆): δ 13.3 (broad singlet, 1H), 8: 45 (m, 2H), 8.37 (d, J = 8 Hz, 1H), 7.99 (d, J = 8 Hz, 1H), 7.85 (dd, J= 7, 2 Hz, 2H), 7.77-7.74 (m, 1H), 7.66-7.65 (m, 2H), 7.50 (t, J 7 Hz, 1H), 7.43-7.25 (m, 8H), 6.68 (d, J = 8 Hz, 1H), 5.35 (dd, J 8, 2 Hz, 1H), 3.43 (d, J = 7 Hz, 2H); MS
25 [+FAB]: [(M+H)⁺], 739.9 (70%), 741.9 (100%), 743.9 (90%); MS High resolution (FAB)+ve, calc mass for C₃₆H₂₄Br₂NO₃S₂ 739.95644; measured mass 739.96224,
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mass deviation 5.80 mmu. Anal. Calc. for C₃₆H₂₃Br₂NO₃S₂: C, 55.58, H, 3.11, N, 1.80. Found: C, 55.38, H, 3.37, N, 1.92.

Example 135.

5 (R)-2-[2,6-Dibromo-4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid

Prepared from of 2,6-dibromo-4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 59) and commercially available (S)-lactic acid, methyl ester. White solid: mp 129-196°C dec; Opt. rot. [α]₂₅/D = + 4.312° (8.812 mg/mL, CHCl₃); NMR (DMSO-d₆); δ 13.12 (broad s, 1H), 8.12 (d, J = 8, 1 Hz, 1H), 8.06 (d, J = 7 Hz, 1H), 7.82 (q, J = Hz, 2H), 7.75 (ddd, J = 8, 7, 1 Hz, 1H), 7.62-7.49 (m, 3H), 7.27 (ddd, J = 8, 7, 1 Hz, 1H), 6.61 (d, J = 8 Hz, 1H), 5.12 (q, J = 7 Hz, 1H), 1.63 (d, J = 7 Hz, 3H); MS (+FAB): [M⁺], 2 bromine isotope pattern, 680 (45%), 682 (100%), 684 (60%); Anal. Calc. for C₂₅H₁₅Br₂IO₃S: C, 44.02, H, 2.22, N, 0.00; Found: C, 44.66, H, 2.54, N, 0.21.

Example 136.

(R)-2-[2,6-Dibromo-4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

20 Prepared from of 2,6-dibromo-4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 59) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: [α]₂₅/D = + 31.791° (9.940 mg / mL CHCl₃); NMR (CDCl₃); δ 8.23 (ddd, J = 8, 1, 1 Hz), 7.81 (ddd, J = 8, 1, 1 Hz, 1H), 7.64 (ddd, J = 8, 7, 1 Hz, 1H), 7.58 (dd, J = 9, 2 Hz, 2H), 7.52-7.39 (m, 7H), 7.37-7.28 (m, 2H), 6.68 (ddd, J = 8, 1, 1 Hz, 1H), 5.48 (t, J = 7 Hz, 1H, -CH), 3.5 (d, J = 7 Hz, 2H); MS (+FAB): [M⁺], 2 bromine isotope pattern, 756 (65%), 758 (100%), 760 (90%); Anal. calc. for C₃₁H₁₉Br₂IO₃S: C, 49.10, H, 2.53, N, 0.00. Found: C, 50.75, H, 3.00, N, 0.09.

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Example 137.**2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-pyridin-3-yl-propionic acid**

Prepared from 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 21) and 3-pyridin-3-yl-propionic acid, ethyl ester (Example 104). White solid: NMR (DMSO-d₆); δ 8.98 (s, 1H), 8.82 (d., J = 5 Hz, 1H), 8.57 (d, J = 8 Hz, 1H), 8.28 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.96 (dd, J = 8, 6 Hz, 1H), 7.82 (d, J = 2 Hz, 1H), 7.79 (m, 1H), 7.78 (d, J = 2 Hz, 1H), 7.62 (dd, J = 8, 1 Hz, 1H), 7.57-7.50 (m, 2H), 7.27 (dd, J = 8, 1 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 5.45 (dd, J = 6, 2, 1H), 3.60 (m, 2H); MS (+FAB): [M+H]⁺, 3 bromine isotope pattern, 710, 712, 714, 716; Anal. Calc. for C₃₀H₁₈Br₃NO₃S•HCl: C, 48.13, H, 2.56, N, 1.87. Found: C, 48.12, H, 2.86, N, 1.65.

Example 138.**(R)-2-[2,6-Dimethyl-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid**

Prepared from of 2,6-dimethyl-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 25) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: NMR (DMSO-d₆); δ 13.0 (broad band, 1H), 8.18 (d, J = 8 Hz, 1H), 7.91 (d, J = 8 Hz, 1H), 7.61 - 7.53 (m, 2H), 7.43 (ddd, J = 8, 7, 1 Hz, 1H), 7.45 - 7.28 (m, 5H), 7.25 - 7.21 (m, 1H), 7.01 (ddd, J = 8, 7, 1 Hz, 1H), 6.95 (d, J = 5 Hz, 2H), 6.53 (d, J = 8 Hz, 1H), 4.75 (t, J = 7 Hz, 1H), 3.32 - 3.24 (m, 2H), 2.87 (s, 3H), 2.56 (s, 3H), 2.18 (s, 3H); MS(EI): [M+]⁺ 516; Anal. Calc. for C₃₄H₂₈O₃S: C, 79.04, H, 5.46, N, 0.00. Found: C, 79.13, H, 5.41, N, 0.11.

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Example 139.**(2R)-2-[4-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenoxy]-3-phenyl-propionic acid**

Prepared from of 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenol (Example 40) and (S)-2-hydroxy-3-phenylpropionic acid, methyl

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ester (Example 96). White solid: NMR (DMSO-d₆); δ 13.08 (broad s, 1H), 8.27 (d, J = 8 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 7.76 (ddd, J = 8, 8, 1, 1H), 7.66-7.58 (m, 2H), 7.43 (ddd, J = 8, 8, 1 Hz, 1H), 7.40-7.34 (m, 4H), 7.31-7.25 (m, 1H), 7.12 (s, 2H), 7.08 (ddd, J = 8, 8, 1, 1H), 6.36 (d, J = 8 Hz, 1H), 4.55 (t, J = 7 Hz, 1H), 3.45 (septuplet, J = 7 Hz, 2H), 3.32 (d, J = 7 Hz, 2H), 1.14 (d, J = 7 Hz, 3H), 1.09 (d, J = 7 Hz, 3H), 1.05 (d, J = 7 Hz, 3H), 1.03 (d, J = 7 Hz, 3H); MS (+FAB): [M⁺] 636 (95%), 638 (100%); Anal. Calc. for C₃₇H₃₃BrO₃S: C, 69.70, H, 5.11, N, 0.00. Found: C, 69.48, H, 5.11, N, 0.11.

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Example 140.

(R)-2-[4-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenoxy]-propionic acid

Prepared from of 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenol (Example 40) and commercially available (S)-lactic acid, methyl ester. White solid: mp: 214-215°C; NMR (CDCl₃); δ 8.37 (ddd, J = 8, 1, 1, 1H), 7.80 (d, J = 8 Hz, 1H), 7.70 (ddd, J = 8, 1, 1 Hz, 1H), 7.66 (ddd, J = 8, 8, 1, 1H), 7.48 (ddd, J = 8, 8, 1 Hz, 1H), 7.37 (ddd, J = 8, 8, 1 Hz, 1H), 7.18 (s, 2H), 7.01 (ddd, J = 8, 8, 1 Hz, 1H), 6.53 (d, J = 8 Hz, 1H), 4.75 (q, J = 7 Hz, 1H), 3.47 (septuplet, J = 7 Hz, 1H), 3.41 (septuplet, J = 7 Hz, 1H), 1.71 (d, J = 7 Hz, 3H), 1.25 (d, J = 7 Hz, 6H), 1.20 (d, J = 7 Hz, 3H), 1.19 (d, J = 7 Hz, 3H); MS (EI): 560 (90%), 562 (100); Anal. Calc. for C₃₁H₂₉BrO₃S: C, 66.31, H, 5.21, N, 0.00. Found: C, 65.90, H, 5.18, N, 0.02.

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Example 141.

(R)-2-[2,6-Dibromo-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Prepared from 2,6-dibromo-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 62) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96). White solid: mp 117-122°C: [α]_D²⁵ = +34.13° (9.963 mg/mL CHCl₃); NMR (DMSO-d₆); δ 8.17 (d, J = 8 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 7.63-7.58 (m,

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1H), 7.57 (dd, J = 6, 2 Hz, 2H), 7.52-7.46 (m, 2H), 7.42-7.38 (m, 3H), 7.37-7.28 (m, 3H), 7.16-7.10 (dt, J = 1, 6 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 5.45 (t, J = 7 Hz, 1H, CH), 3.59 (d, J = 7 Hz, 2H), 2.98 (s, 3H); MS (EI): [M+], 643.6 (20%), 644.4 (50%), 645.5 (100%) 647.7 (30%); Anal. Calc. for C₃₂H₂₂Br₂O₃S: C, 59.46, H, 3.43, N, 0.00. Found: C, 59.34, H, 3.24, N, 0.04.

Example 142.

(R)-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-phenyl-acetic acid

10 Prepared from 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 21) and commercially available methyl (S)-(+)-mandelate. White solid: mp 135-137°C: MS (FAB-): [M-H]⁻, 693; Anal. Calc. for C₃₀H₁₇Br₃O₃S: C, 51.68, H, 2.46, N, 0.00. Found: C 51.57, H, 2.89, N, 0.14.

Example 143.

(S)-2-[2-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid

15 Prepared from of 2-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 68) and commercially available (R)-lactic acid, methyl ester.

20 White solid: mp 132-134°C: MS (+EI): [M+], 2 bromine isotope pattern, 554, 556, 558; Anal. Calc. for C₂₅H₁₆Br₂O₃S: C, 53.98, H, 2.90, N, 0.00. Found: C, 52.97, H, 2.98, N, 0.04.

Example 144.

25 (R)-2-[2-bromo-5-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid

Prepared from of 2-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (Example 68) and commercially available (R)-lactic acid, methyl ester. White solid: mp 133-134.5°C: MS (-ESI): [M-H]⁻, 2 bromine isotope pattern 553,

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555, 557; Anal. Calc. for C₂₅H₁₆Br₂O₃S: C, 53.98, H, 2.90, N, 0.00. Found: C, 53.18, H, 2.82, N, 0.04.

Example 145.

- 5 (R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid, methyl ester

Diethylazodicarboxylate (0.293 mL, 1.86 mmol) was added dropwise to a stirred, ambient temperature suspension of 2,6-dibromo-4-(6-bromo-benzo[b]-naphtho[2,3-d]thiophen-11-yl)-phenol (0.700 g, 1.24 mmol), (S)-(+)-2-hydroxy-1,3-
10 dioxo-2-isoindolinebutyric acid, methyl ester (0.490 g, 1.86 mmol), triphenylphosphine (0.488 g, 1.86 mmol) and benzene (5.5 mL) under a dry nitrogen atmosphere. Dissolution occurred and the solution was heated in an 80°C oil bath for 1.5 h. Upon cooling to room temperature, the reaction mixture was diluted with dicloromethane and silica gel (20 mL) was added. The reaction mixture was
15 concentrated and the silica adsorbate was flash chromatographed (83:17 petroleum ether : ethyl acetate) to provide the title compound as a white solid (0.822 g, 81%): mp 221-222°C; NMR (DMSO-d₆); δ 8.29 (d, J = 8 Hz, 1H), 8.08 (d., J = 8 Hz, 1H), 7.98 (ddd, J = 8, 7, 1 Hz, 2H), 7.87-7.83 (m, 4H), 7.80 (ddd, J = 8, 7, 1 Hz, 1H), 7.66-7.58 (m, 2H), 7.53 (ddd, J = 8, 7, 1 Hz, 1H), 7.29 (ddd, J = 8, 7, 1 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 5.16 (t, 1H), 3.94 (m, 2H), 3.71 (s, 3H), 2.50 (m, 2H); MS (FAB+): [M+], 3 bromine isotope pattern, 805 (22%), 807 (88%), 809 (100%), 811 (42 %);
20 Anal. Calc. for C₃₅H₂₂Br₃NO₅S: C, 52.01, H, 2.74, N, 1.73. Found: C, 52.02, H, 2.70, N, 1.73.

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Example 146.

(R)-2-(4-Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dibromo-phenoxy)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid

Iodotrimethylsilane (0.203 mL, 1.43 mmol) was added to a rt, stirred solution of (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-
30 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid, methyl ester (0.770 g, 0.953

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mmol) in methylene chloride (8 mL) under a dry nitrogen atmosphere. After 2 h, iodotrimethylsilane (3 x 0.203 mL, 4.29 mmol) was added to the resulted dark brown solution at rt three times every 12 h. The solution was quenched with water (0.4 mL), concentrated, chased with benzene (3 x 50 mL). The resulted residue was dissolved
5 in ethyl acetate (60 mL) and silica gel (acid washed, 8 mL) was added. Solvent was removed and the adsorbate was flash chromatographed (eluent 7:3 pet. ether: ethyl acetate) to provide the title compound as a yellow solid (0.304 g, 45 %): mp: 222-223°C; NMR (CDCl₃); δ 8.37 (s, 1H), 7.95(d, J = 8 Hz, 1H), 7.89-7.85 (m, 2H), 7.79 (dd, J = 8, 1 Hz, 1H), 7.78-7.71 (m, 2H), 7.64 (d, J = 10 Hz, 1H), 7.62 (d, J = 10 Hz,
10 1H), 7.59 (dd, J = 8, 1 Hz, 1H), 7.55 (ddd, J = 8, 7, 1 Hz, 1H), 7.46 (ddd, J = 8, 7, 1 Hz, 1H), 7.40 (ddd, J = 8, 7, 1 Hz, 1H), 7.19(ddd, J = 8, 7, 1 Hz, 1H), 6.88(d, J = 8 Hz, 1H), 5.27 (t, J = 7 Hz, 1H, 1H, CH), 4.12 (m, 2H), 2.65 (t, J = 6 Hz, 2H); MS (FAB-): [M-H]⁻, 2 bromine isotope pattern, 713, 714, 716; Anal. Calc. for C₃₄H₂₁Br₂NO₅S: C, 57.08, H, 2.96, N, 1.96. Found: C, 56.43, H, 2.74, N, 1.90.

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Example 147.

(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid

Iodotrimethylsilane (2.8 mL, 1 N in methylene chloride) was added dropwise
20 to a -10°C, stirred solution of (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid, methyl ester (0.770 g, 0.953 mmol) in methylene chloride (14 mL) under a dry N₂ atmosphere. The solution was allowed to warm to ambient temperature and was stirred overnight. The reaction mixture was quenched, further diluted with water (100
25 mL), and partitioned between water and methylene chloride (2 x 75 mL). Methylene chloride extracts were concentrated and triturated with pet. ether. It was then recrystallized from acetic acid to provide the title compound as a grey solid (0.228 g, 52%): mp 215-217°C; NMR (CDCl₃); δ 8.35 (d, J = 8 Hz, 1H), 7.89-7.86 (m, 2H), 7.82 (dd, J = 8, 1 Hz, 1H), 7.76-7.71 (m, 2H), 7.67(ddd, J = 8, 7, 1 Hz, 1H), 7.63-7.59
30 (m, 3H), 7.58 (ddd, J = 8, 7, 1 Hz, 1H), 7.42 (ddd, J = 8, 7, 1 Hz, 1H), 7.20 (ddd, J =

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8, 7, 1 Hz, 1H), 6.81(d, J = 8 Hz, 1H), 5.27 (t, J = 7 Hz, 1H, 1H), 4.12 (m, 2H), 2.65 (t, J = 7 Hz, 2); MS (EI): [M+], 3 bromine isotope pattern, 791 (75%), 793 (98%), 795 (100%), 797 (38%); Anal. Calc. for C₃₄H₂₀Br₃NO₅S: C, 51.41, H, 2.54, N, 1.76. Found: C, 51.65, H, 2.37, N, 1.70.

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Example 148.

(R)-2-(4-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid

Iodotrimethylsilane (1.31 mL, 9.23 mmol) was added dropwise to a 0°C, stirred solution of (R)-2-(4-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy)-4-(1, 3-dioxo-1, 3-dihydro-isoindol-2-yl)-butyric acid, methyl ester (1.17 g, 2.05 mmol) in methylene chloride (15 mL) under a try N₂ atmosphere. After 1 h. the solution was allowed to warm to ambient temperature. After 1 h. the reaction mixture was quenched with 10% aqueous sodium bisulfide and further diluted with water (100 mL). Aqueous mixture was extracted with ethyl acetate (150 mL). The ethyl acetate extract was washed with water, dried with brine and anhydrous MgSO₄, and concentrated to provide a white solid. The solid was recrystallized from aqueous acetic acid and purified by HPLC (Dynamax C18 Column, 90:10 acetonitrile:water (both with 0.1% TFA) to provide the title compound as a light yellow solid (0.420 g, 32%): mp 145-14°C 7: NMR (CDCl₃); δ 8.31 (s, 1H), 7.92 (d, J = 8 Hz, 1H), 7.87-7.84 (2 distored d, J = 8 Hz, 2H), 7.75 (d, J = 8 Hz, 1H), 7.72-7.69 (2 distored d, J = 8 Hz, 2H), 7.59 (d, J = 8 Hz, 1H), 7.49 (ddd, J = 8, 7, 1 Hz, 1H), 7.39-7.33 (m, 2H), 7.29-7.22 (m, 2H), 7.15 (ddd, J = 8, 7, 1 Hz, 1H), 7.05 (dd, J = 9, 8 Hz, 1H), 7.01 (dd, J = 9, 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 4.99 (t, J = 6 Hz, 1H), 4.09 (t, J = 6 Hz, 2H), 2.52 (q, J = 6 Hz, 2H); MS (+FAB): [M+H]⁺, 558; Anal. Calc. for C₃₄H₂₃NO₅S: C, 73.23, H, 4.16, N, 2.51. Found: C, 71.82, H, 4.00, N, 2.61.

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Example 149.

(R)-2-[4-(3-Carboxymethoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid

Diethylazodicarboxylate (DEAD, 0.133 mL, 0.845 mmol) was added to a stirred, room temperature solution of 11-(4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-yloxy]-acetic acid methyl ester (0.140 g, 0.338 mmol), L-3-phenyllactic acid, methyl ester (0.133 g, 0.845 mmol), triphenylphosphine (0.222 g, 0.845 mmol) and benzene (1.5 mL) under a dry nitrogen atmosphere. Dissolution occurred and the solution was heated in an 80°C oil bath for 6 h. More diethylazodicarboxylate (DEAD, 0.053 mL, 0.338 mmol), L-3-phenyllactic acid, methyl ester (0.070 g, 0.338 mmol) and triphenylphosphine (0.103 g, 0.338 mmol) were added. The reaction mixture was cooled to room temperature after 5.5h. The reaction mixture was diluted with ether and silica gel was added. The reaction mixture was concentrated and the silica adsorbate was flash chromatographed (gradient 99:1 to 98:2 dichloromethane:acetonitrile) to provide a white solid (0.190g). This solid was recrystallized from acetonitrile containing 0.1% of trifluoroacetic acid to provide a white solid (144 mg). 1.0 M solution of boron tribromide (1.4 mL, 1.4 mmol) in dichloromethane was added to a stirred, -78°C solution of this solid in dichloromethane (3.0 mL). After 45 min the reaction mixture was warmed to room temperature. After 3.5 h, the reaction mixture was recooled to -78°C and an additional amount of 1.0N boron tribromide (0.8 mL, 0.8 mmol) was added. The reaction mixture was warmed to room temperature. After an additional 2h, water was added and the reaction mixture was extracted with ethyl acetate. The ethyl acetate phase was concentrated and purified by prep HPLC (reverse phase: 7:3 acetonitrile: water with 0.1 % trifluoroacetic acid). The resultant compound (13 mg) was recrystallized from acetic acid/water to provide the title compound as a white solid (0.005 g, 2%) : mp: 259-260°C: NMR (DMSO-d₆); δ 13.2 (broad s, 2H), 8.54 (s, 1H), 8.02 (d, J = 8 Hz, 1H), 7.88-7.81 (m, 4H), 7.55-7.44 (m, 4H), 7.25 (dd, J = 9, 2 Hz, 2H), 7.11-7.04 (m, 2H) 6.79 (dd, J = 9, 2 Hz, 1H), 6.52 (d, J = 9 Hz, 1H), 5.03 (dd, J = 8, 2 Hz, 1H), 4.75

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(s, 2H), 3.92 (m, 2H), 2.32 (m, 2H); MS (FAB+): 632 (10%, M+H); Analytical HPLC: 98.8% pure.

Example 150.

5 (R)-2-[4-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid

Boron tribromide (1 M solution in methylene chloride, 10.4 mL, 10.4 mmol) was added dropwise to a -10°C, stirred solution of (R)-2-[4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid, methyl ester (1.35 g, 2.08 mmol) in methylene chloride (35 mL) under a try N₂ atmosphere. After 1 h. the solution was allowed to warm to ambient temperature. After 1 h. the reaction mixture was quenched, further diluted with water (100 mL), and partitioned between water and methylene chloride. Methylene chloride extracts were concentrated to give a solid, The solid was separated and purified by HPLC (Dynamax C18 Column, 95:5 acetonitrile:water (both with 0.1% TFA) to provide the title compound as a light yellow solid (0.420 g, 32%): mp >69°C (dec): NMR (CDCl₃): δ 8.32 (d, J = 8 Hz, 1H), 7.86-7.84 (2 d, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 1H), 7.72-7.70 (d, J = 8 Hz, 2H), 7.64-7.59 (m, 2H), 7.43-7.36 (m, 2H), 7.25-7.16 (m, 3H), 7.05 (dd, J = 9, 8 Hz, 1H), 7.01 (dd, J = 9, 8 Hz, 1H), 6.68(d, J = 8 Hz, 1H), 4.99 (t, J = 6 Hz, 1H), 4.09 (t, J = 6 Hz, 2H), 2.52 (q, J = 6 Hz, 2H); MS (EI): [M+], 1 bromine isotope pattern, 635 (90%), 637 (100%); Anal. Calc. for C₃₄H₂₂BrNO₅S: C, 64.16, H, 3.48, N, 2.20. Found: C, 64.19, H, 4.04, N, 2.08.

Example 151.

25 (R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-succinic acid dimethyl ester

Diethylazodicarboxylate (0.254 mL, 1.61 mmol) was added dropwise to a stirred, room temperature suspension of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (0.600 g, 1.10 mmol), dimethyl (S)-(-)-malate (0.213 mL, 1.61 mmol) and triphenylphosphine (0.421 g, 1.61 mmol) in benzene (7.5 mL)

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under a dry nitrogen atmosphere. The solution was heated in an 79°C oil bath for 23 h. Additional Dimethyl (S)-(-)-malate (0.043 mL, 0.321 mmol) and triphenylphosphine (0.084 g, 0.321 mmol) and diethylazodicarboxylate (0.050 mL, 0.321 mmol) were added and the reaction mixture was heated for an additional 10 hours. The reaction mixture was cooled to room temperature, diluted with methylene chloride combined with silica gel (20 mL) and concentrated. The silica adsorbate was flash chromatographed (92 : 8 petroleum ether : ethyl acetate) to provide the title compound as a white solid (0.389 g, 51%): mp 118-121°C: NMR (CDCl₃); δ 8.36 (dd, J = 8, 0.5 Hz, 1H), 7.83 (dd, J = 8, 0.5 Hz, 1H), 7.68 (ddd, J = 8, 7, 1 Hz, 1H), 7.61 - 7.59 (m, 3H), 7.55 - 7.43 (m, 2H), 7.26 - 7.21 (m, 1H), 6.79 (d, J = 8 Hz, 1H), 5.46 (t, J = 6 Hz, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.32 - 3.30 (m, 1H); MS (EI): [M⁺], 3 bromine isotope pattern, 704 (5%), 706 (15%), 708 (15%), 710 (4%); Anal. Calc. for C₂₈H₁₉Br₃O₅S: C, 47.55, H, 2.71, N, 0.00. Found: C, 47.93, H, 2.65, N, 0.14.

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Example 152.

(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-succinic acid

A solution of (R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-succinic acid, dimethyl ester (0.317 g, 0.448 mmol) in 4M HCl in dioxane (5 mL) was combined with water (5 mL) and concentrated HCl (1 mL) in a sealed pressure bottle and heated for 9 hours. After remaining at ambient temperature for an additional 14 hours the reaction mixture was partitioned between water and ether. The layers were separated and acid treated silica gel (7 mL) was added to the ether layer. The solvent was removed and the adsorbate was purified by flash chromatography (acid treated silica gel, eluant 80 : 20 pet. ether : ethyl acetate) to provide the title compound as a white solid (0.142 g, 47%), mp 163-164°C; [a]_{D25}=+14.16° (8.825 mg/mL, methanol); NMR (DMSO-d₆); δ 13.6 - 13.2 (broad singlet, 1H), 12.7 - 12.6 (broad singlet, 1H), 8.28 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.82 - 7.78 (m, 3H), 7.65 - 7.57 (m, 2H), 7.52 (dd, J = 7, 1 Hz, 1H), 7.31 (dd, J = 7, 1, 1H), 6.70 (d, J = 8 Hz, 1H), 5.32 (t, J = 8 Hz), 3.67 (m, 2H); MS (-FAB) [M-H]⁻;

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3 bromine pattern detected, 675(25%), 677(10%), 679(25%), 681(10%); Anal. Calc. for C₂₆H₁₅Br₃O₅S: C, 45.78, H, 2.23, N, 0.00. Found: C, 46.42, H, 2.40, N, 0.05.

Example 153.

5 2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(4-fluoro-phenyl)-propionic acid tert-butyl ester

Diisopropylamine (distilled over CaH₂, 0.169 mL, 1.2 mmol) was added to anhydrous tetrahydrofuran (0.65 mL) and cooled to -74°C under a dry argon atmosphere. n-Butyllithium (2.5M in hexane, 0.516 mL, 1.29 mmole) was added
10 dropwise and the mixture was warmed to 0°C for 10 minutes then recooled to -74°C. Hexamethylphosphoramide (0.83 mL) was added followed 5 minutes later by the slow (0.5 hour) dropwise addition of a solution of (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid, tert-butyl ester (0.715g, 1.06 mmole) in anhydrous tetrahydrofuran (2.8 mL). After stirring one hour
15 at -75°C, 4-fluorobenzylbromide (0.158 mL, 1.29 mmol) was added dropwise. After stirring 1 hour at -80°C the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with dilute aqueous ammonium chloride and was partitioned between water (100 mL) and a 1 : 1 methylene chloride : ether solution (130 mL). After one more extraction with
20 methylene chloride (50mL) the organic layers were combined, silica gel was added, and the solvents removed. The adsorbate was purified by flash chromatography (eluent 7 : 3 pet ether : methylene chloride) and HPLC (Column: Waters Silica Prep Pak; gradient, 99 : 1 to 95 : 5 petroleum ether : ethyl acetate ; Flow rate = 225 mL/min) to provide the title compound as a white solid (0.265 g, 32%): mp: 80-
25 100°C; NMR(CDCl₃); δ 8.35 (dd, J = 8, 1 Hz, 1H), 7.83 (dd, J = 6, 1 Hz, 1H), 7.66 (ddd, J = 6, 5, 1 Hz, 1H), 7.58 (dd, J = 4, 2 Hz, 2H), 7.53 - 7.38 (m, J = 2 Hz, 5H), 7.18 (ddd, J = 7, 1, 1, 1H), 7.04 (t, J = 9 Hz, 2H), 6.83 (d, J = 8 Hz, 1H), 5.31 (t, J = 6 Hz, 1H), 3.49 (t, J = 6 Hz, 2H), 1.40 (s, 9H); MS (FAB+): [M⁺], 3 bromine pattern, 782 (20%), 784 (70%), 786 (80%), 788 (35%); Anal. Calc. for C₃₅H₂₆Br₃FO₃S: C,
30 53.53, H, 3.34, N, 0.00. Found: C, 53.25; H, 3.21, N, 0.04.

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Example 154.

(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-naphthalen-2-yl-propionic acid tert-butyl ester

- 5 Diisopropylamine (distilled over CaH₂, 0.233 mL, 1.78 mmol) was added to anhydrous tetrahydrofuran (0.91 mL) and cooled to -74°C under a dry argon atmosphere. n-Butyllithium (2.5M in hexane, 0.71 mL, 1.78 mmole) was added dropwise and the mixture was warmed to 0°C for ca. 20 minutes then recooled to -75°C. Hexamethylphosphoramide (2 mL) was added followed 10 minutes later by the
- 10 slow (0.5 hour) dropwise addition of a solution of (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid, tert-butyl ester (1.004 g, 1.48 mmole) in anhydrous tetrahydrofuran (3 mL). After stirring one hour at -75°C, 2 bromomethylnaphthalene (0.393g, 1.78 mmol) was added dropwise. After stirring 0.5 hour at -80°C the reaction mixture was allowed warm to room temperature
- 15 overnight. The reaction mixture was quenched with dilute aqueous ammonium chloride and was partitioned between water (100 mL) and a 1 : 1 methylene chloride : ether solution (200 mL). After one more extraction with methylene chloride the organic layers were combined, washed with water (100 mL) and purification by flash chromatographed (eluent 7 : 3 pet ether : ethyl acetate) and HPLC (2 times) (First
- 20 column: Waters Silica Prep Pak; isocratic, 98 : 2 hexane : ethyl acetate; Flow rate = 225 mL/min; Second column: Waters Silica Prep Pak; gradient, 75 : 25 to 60 : 40 petroleum ether : methylene chloride) to provide the title compound as a white solid (0.280 g, 23%); NMR (CDCl₃); δ 8.35 (d, J = 8 Hz, 1H), 7.88-7.80 (m, 5H), 7.66 (ddd, J = 6, 5, 1 Hz, 1H), 7.61 (d, J = 2 Hz, 1H), 7.60 (d, J = 2 Hz 1H) 7.58-7.56 (m,
- 25 2H), 7.51-7.41 (m, 4H), 7.18 (ddd, J = 7, 1, 1 Hz, 1H), 6.83 (dd, J = 7, 1 Hz, 1H) 5.44 (t, J = 8 Hz, 1H), 1.34 (s, 9H); MS (FAB+): [M⁺], 3 bromine pattern, 814 (30%) 816 (95%) 818 (100%) 820 (42%); Anal. Calc. for C₃₉H₂₉Br₃O₃S: C, 57.30; H, 3.58, N, 0.00. Found: C, 57.55; H, 3.75, N, 0.02.

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Example 155.**2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(4-fluoro-phenyl)-propionic acid**

A suspension of 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(4-fluoro-phenyl)-propionic acid tert-butyl ester (0.232g 0.295 mmol) in trifluoroacetic acid (5 mL) was heated at 55°C for 11 hours. After cooling to room temperature the reaction mixture was poured into water (60mL) and extracted with ether. The combined ether extracts were washed with water and brine, concentrated, and dried in vacuo at 60°C to provide the title compound as an off white solid (0.187 g, 98%): NMR (CDCl₃); δ 8.36 (d, J = 7 Hz, 1H), 7.82 (d, J = 7 Hz, 1H), 7.68 (ddd, J = 8, 6, 2 Hz, 1H), 7.58 (dd, J = 8, 2 Hz, 2H), 7.55-7.48 (m, 2H), 7.45-7.35 (m, 3H), 7.15 (dt, J = 7, 1, 1H), 7.03 (tt J = 10, 3, 1, 2H), 6.71 (d, J = 8 Hz, 1H), 5.44 (t, J = 6 Hz, 1H), 3.56 (d, J = 7 Hz, 2H); MS (+ FAB): [M⁺], 3 bromine isotope pattern, 726 (15%), 728 (30%) 730 (35%) 732 (15%); Anal. Calc. for C₃₁H₁₈Br₃FO₃S: C, 51.06, H, 2.49, N, 0.00. Found: C, 50.80, H, 2.46, N, 0.10.

Example 156.**2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-naphthalen-2-yl-propionic acid**

A solution of 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-naphthalen-2-yl-propionic acid, tert butyl ester (0.221 g, 0.270 mmol) in trifluoroacetic acid (10 mL) was heated to 50°C for 15 hours. The mixture was cooled to room temperature and combined with water. Ether was added and the resulting organic suspension was separated from the water layer and concentrated. The residue was dried in vacuo at 46C to provide the title compound as an off white solid (0.186 g, 90%) mp 270-271°C; NMR (DMSO-d₆); δ 13.25 (broad singlet, 1H), 8.28 (d, J = 8 Hz, 1H), 8.06 (d, J = 8 Hz, 1H), 7.91(m, 4H), 7.81(d, J = 2 Hz, 1H), 7.79(d, J = 2 Hz, 1H) 7.82-7.77(m, 1H), 7.63-7.47(m, 6H), 7.25 (dd, J = 7, 1 Hz, 1H), 6.64 (d, J = 8 Hz, 1H) 5.42 (t, J = 7 Hz, 1H), 3.59 (d, J = 7 Hz, 2H); MS (FAB+): [M⁺], 3 bromine pattern , 757.8 (21%) 759.8 (100%) 761.8 (100%) 763.8 (50%);

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Anal. Calcd. for C₃₁H₁₉Br₃O₃S: C, 55.07; H, 3.04, N, 0.00. Found: C, 55.36; H, 2.89, N, 0.06.

Example 157.

5 Diethyl Trifluoromethanesulfonoxymethylphosphonate

Prepared according to the procedure of D.P. Phillion and S.S. Andrew *Tet. Lett.* **1986**, 1477-1480. A solution of trifluoromethanesulfonic anhydride (11.6 mL, 68.9 mmol) in methylene chloride (45 mL) was added dropwise to a stirred, -10 °C solution of diethyl hydroxymethylphosphonate (10.82 g, 64.4 mmol) and pyridine
10 (5.76 mL, 68.9 mmol) in methylene chloride (170 mL) under N₂ over a period of 20 min. The mixture was stirred at -10 °C for 1h. and placed in the freezer (-15 to -20 °C) overnight. The reaction mixture was diluted with cold methylene chloride and washed with cold 1 N HCl and ice water. The organic layer was separated, dried with brine, anhydrous MgSO₄ and concentrated to provide an oil (12.58 g, 65 %): MS
15 (+FAB): [M+H]⁺, 423 .

Example 158.

{2,6-Dibromo-4-[6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl]}-phenoxymethyl}-phosphonic acid diethyl ester

20 A solution of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (1.00 g, 1.78 mmol) in THF (5 mL) was added dropwise to a stirred, 0°C solution of 80 % sodium hydride (0.08 g, 2.67 mmol) in THF (10 mL) under a dry nitrogen atmosphere over a period of 15 min. After the mixture was stirred in an 0°C oil bath for 40 min., a solution of diethyl trifluoromethanesulfonoxymethyl-
25 phosphonate (0.80 g, 2.67 mmol) was added dropwise over a period of 15 min. The reaction mixture was then warmed to, and stirred at, ambient temperature for 1 h. The reaction mixture was quenched and diluted with water (80 mL). The resulting solid was filtered, washed with water and triturated with pet. ether. The solid was dried in vacuo at 50°C to provide the title compound as a white solid (1.12 g, 88%): mp 178-
30 180°C: NMR (CDCl₃); δ 8.36 (d, J = 9 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.68 (ddd, J

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= 7, 6, 1 Hz, 1H), 7.62 (s, 2H), 7.57-7.49 (m, 2H), 7.45 (ddd, J = 8, 7, 1 Hz, 1H), 7.18 (ddd, J = 8, 7, 1 Hz, 1H), 6.73 (d, J = 8, Hz, 1H), 4.61 (s, 2H), 4.41 (q, 4H), 1.49 (t, 6H, CH₃); MS (EI): [M⁺], 3 bromine isotope pattern, 710 (35%), 712 (95 %) 714 (100%), 716 (40%); Anal. Calc. for C₂₇H₂₂Br₃O₄PS: C, 45.47, H, 3.11, N, 0.00.

5 Found: C, 45.30, H, 2.95, N, 0.07.

Example 159.

[4-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxyethyl]-phosphonic acid diethyl ester

10 A solution of 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (1.00 g, 3.06 mmol) in THF (5 mL) was added dropwise to a stirred, 0°C solution of 80 % sodium hydride (0.138 g, 4.95 mmol) in THF (10 mL) under a dry nitrogen atmosphere over a period of 15 min. After the mixture was stirred in an 0°C oil bath for 1 h., a solution of diethyl trifluoromethanesulfonoxymethylphosphonate (1.4 g, 4.95 mmol) was
15 added dropwise over a period of 15 min. The reaction mixture was then warmed to and stirred at ambient temperature for 2 h. The reaction mixture was quenched and diluted with water (150 mL). Aqueous mixture was extracted with ethyl acetate (2 X 150 mL). The ethyl acetate extracts were washed with water, dried with brine and anhydrous MgSO₄, and concentrated to provide a white solid. The solid was purified
20 by flash chromatography (eluent 7:3 pet. ether: ethyl acetate) to provide the title compound as a white solid (0.922 g, 63 %): mp 129-130°C; MS (EI): [M⁺], 476 (100% MI); Anal. Calc. for C₂₇H₂₅O₄PS: C, 68.05, H, 5.29, N, 0.00. Found: C, 66.58, H, 5.34, N, 0.00.

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Example 160.

3-Phenyl-1-hydroxy-1-propylphosphonic acid, diethyl ester

Aluminum oxide (15 g) was added to a stirred, ambient temperature solution of hydrocinnamaldehyde (3.93 mL, 28.3 mmol) and diethylphosphite (3.72 mL, 28.3 mmol) in methylene chloride (30 mL). The mixture was stirred at ambient
30 temperature for 2 days. The reaction mixture was filtered and dichloromethane filtrate

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was concentrated and triturated with petroleum ether to provide the title compound as a white solid (4.10 g, 53%): mp 60-61°C: MS (+FAB): [M+H]⁺, 273 (100%, MI); Anal. Calc. for C₁₃H₂₁O₄P: C, 57.35, H, 7.77, N, 0.00. Found: C, 57.48, H, 7.87, N, 0.04.

5

Example 161.

{1-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propyl}-phosphonic acid, diethyl ester

Diethylazodicarboxylate (0.420 mL, 2.67 mmol) was added dropwise to a stirred, ambient temperature suspension of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (1.00 g, 1.78 mmol), 3-phenyl-1-hydro-1-propylphosphonic acid, diethyl ester (0.730 g, 2.67 mmol), triphenylphosphine (0.700 g, 2.67 mmol) and benzene (9 mL) under a dry nitrogen atmosphere. The solution was heated in an 80°C oil bath for 4 h. Upon cooling to room temperature, the reaction mixture was partitioned between water (80 mL) and dichloromethane (100 mL). Dichloromethane phase was washed with 10 % aq HCl (80 mL) and silica gel (20 mL) was added. Solvent was removed and the silica adsorbate was flash chromatographed (95:5 Dichloromethane : acetonitrile) to provide the title compound as a white solid (1.17 g, 73%): mp 161-162°C: MS (EI⁺): [M⁺], 3 bromine isotope pattern, 814, 816, 818, 820; Anal. Calc. for C₃₅H₃₀Br₃O₄PS: C, 51.43, H, 3.70, N, 0.00. Found: C, 51.36, H, 3.67, N, 0.03.

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Example 162.

[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxyethyl]-phosphonic acid

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Iodotrimethylsilane (0.63 mL, 4.41 mmol) was added dropwise to a stirred, 0°C solution of {2,6-dibromo-4-[6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenoxyethyl}-phosphonic acid diethyl ester (1.05 g, 1.47 mmol) in methylene chloride (29 mL) under a dry nitrogen atmosphere over a period of 10 min. After 1 h at 0°C, the reaction mixture was quenched with water (0.5 mL), stirred at ambient

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temperature for 30 min., and then diluted with water (50mL). The solid was filtered and partitioned in ethyl acetate (100 mL) and 20 % aqueous HCl (60 mL) with stirring for 3 h. The solid was filtered, washed with water and triturated with pet. ether. The solid was dried in vacuo at 100°C to provide the title compound as an off-white solid
5 (0.428 g, 44 %): mp 334-335°C: NMR (DMSO-d₆): δ 8.28 (d, J = 9 Hz, 1H), 8.07 (d, J = 8, Hz, 1H), 7.84 (s, 2H), 7.79 (ddd, J = 8, 7, 1 Hz, 1H), 7.65-7.57 (m, 2H), 7.52 (dd, J = 7, 1 Hz, 1H), 7.32 (ddd, J = 8, 7, 1 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 4.32 (d, J = 1 Hz, 2H); MS (ESI): [M-H]⁻, 3 bromine isotope pattern; Anal. Calc. for C₂₃H₁₄Br₃O₄PS: C, 42.04, H, 2.15, N, 0.00. Found: C, 41.26, H, 2.12, N, 0.05;
10 Karl Fischer: 0.58 mol H₂O.

Example 163.

[4-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy-methyl]-phosphonic acid

Iodotrimethylsilane (0.78 mL, 5.49 mmol) was added to a 0-5 °C, stirred
15 solution of [4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy-methyl]-phosphonic acid diethyl ester (0.871 g, 1.83 mmol) in methylene chloride (24 mL) under a dry N₂ atmosphere over a period of 10 min. After 1 h, the solution was quenched with water (0.6 mL), 10 % aqueous sodium carbonate (100 mL) was added and mixture was washed with methylene chloride. The aqueous layer was acidified with 10% aqueous
20 HCl. The solid was filtered and recrystallized from methanol (75 mL) to provide the title compound as a white solid (0.65 g, 85%): mp 240-242°C: MS (EI): [M⁺], 420; Anal. Calc. for C₂₃H₁₇O₄PS: C, 65.17, H, 4.08, N, 0.00. Found: C, 63.95, H, 3.89, N, 0.41.

25

Example 164.

{1-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propyl}-phosphonic acid

Iodotrimethylsilane (0.56 mL, 3.93 mmol) was added dropwise to a stirred, 0°C solution of {1-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-
30 phenoxy]-3-phenyl-propyl}-phosphonic acid, diethyl ester (1.07 g, 1.31 mmol) in

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methylene chloride (26 mL) under a dry nitrogen atmosphere over a period of 10 min. After 1 h at 0°C, the reaction mixture was quenched with 10 % aq sodium bisulfite (1 mL), stirred at ambient temperature for 30 min. The mixture was partitioned in methylene chloride (100 mL) and water (100 mL). The methylene chloride phase was washed with 18 % aq HCl (100 mL), concentrated, and triturated with pet. ether to afford a crude solid (0.894 g). The solid was then recrystallized from 85 % aq. acetic acid (50 mL) to provide the title compound as a off-white solid (0.466 g, 47%): NMR (CDCl₃); δ 8.33 (d, J = 9 Hz, 1H), 7.76 (d, J = 7 Hz, 1H), 7.59 (ddd, J = 8, 7, 1 Hz, 1H), 7.48-7.40 (m, 3H), 7.36-7.28 (m, 2H), 7.06-6.98 (m, 5H), 6.91-6.83 (m, 1H), 6.77 (d, J = 8 Hz, 1H), 5.47-5.42(m, 1H), 4.50 (s, 2H), 3.05-2.85 (m, 2H), 2.59-2.41 (m, 2H); MS (FAB-): [M-H]⁻, 3 bromine isotope pattern, 756; Anal. Calc. for C₃₁H₂₂Br₃O₄PS: C, 48.91, H, 2.91, N, 0.00. Found: C, 49.29, H, 2.90, N, -0.02.

Example 165.

15 2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetamide

Methanol (10 mL) was purged with ammonia gas for 10 min at 0°C. [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid, methyl ester (0.50 g, 0.787 mmol) was added and the vessel was sealed, warmed to room temperature and stirred for two days. The reaction mixture was concentrated, diluted with ether and filtered. The solid was boiled in ethyl acetate (8 mL), hot filtered and washed with ethyl acetate and pentane and dried in vacuo to provide the title compound as an off white solid (0.22 g, 45%): mp 263-265°C: NMR (DMSO-d₆); δ 8.29 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 7.88 (s, 2H), 7.80 (ddd, J = 8, 7, 1 Hz, 1H), 7.67-7.51 (m, 5H), 7.30 (ddd, J = 8, 7, 1 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 4.56 (s, 2H); MS (EI): [M]⁺, 3 bromine isotope pattern, 617 (30%), 619 (90%) 621 (100%) 623 (40%); Anal. Calc. for C₂₄H₁₄Br₃NO₂S: C, 46.48, H, 2.28, N, 2.26. Found: C, 45.69, H, 2.02, N, 2.14.

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Example 166.**(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionamide**

Three drops of DMF were added to a stirred, room temperature solution of
5 (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid (2.09 g, 2.94 mmol), oxalyl chloride (0.31 mL, 3.53 mmol) and dichloromethane (31 mL) under a dry nitrogen atmosphere. Oxalyl chloride (0.10 mL, 1.14 mmol) was added after 2.5 h and again (0.10 mL, 1.14 mmol) at 6h. After 6.5 h, the reaction mixture was concentrated and dried in vacuo. The solid was dissolved in
10 dichloromethane (25 mL) and added over a 2 minute period to stirred, cold (0°C) concentrated ammonium hydroxide (50 mL). The dichloromethane was removed and the resulting solid was filtered and washed with water and dried in vacuo to provide the title compound as a white solid (1.99 g, 95%); mp 220-222°C: NMR (DMSO-d₆); δ 8.28 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.80 (ddd, 8, 7, 1 Hz, 1H), 7.75 (d, J =
15 2 Hz, 1H), 7.74 (d, J = 2 Hz, 1H), 7.67-7.62 (m, 2H), 7.53-7.48 (m, 2H), 7.41-7.24 (m, 7H), 6.69 (d, J = 8 Hz, 1H), 5.74 (s, 1H, 0.5 eq CH₂Cl₂), 5.23 (t, J = 6 Hz, 1H), 3.46-3.27 (m, 2H); MS (+FAB): [M⁺], 3 bromine isotope pattern, 707 (30%), 709 (75%) 711 (100%) 713 (40%); Anal. Calc. for C₃₁H₂₀Br₃NO₂S•0.56CH₂Cl₂: C, 50.02, H, 2.82, N, 1.85. Found: C, 49.67, H, 2.67, N, 1.96.

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Example 167.**(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-N-hydroxy-3-phenyl-propionamide**

DMF (2 drops) was added to a stirred solution of (R)-2-[2,6-dibromo-4-(6-
25 bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid (0.736 g, 1.03 mmol), oxalyl chloride (0.11 mL, 1.27 mmol) and dichloromethane (11 mL). After 1 h, the solvent was removed. The residue was dissolved in chloroform (3.5 mL) and added dropwise to a rapidly stirred, 0°C suspension of hydroxylamine hydrochloride (0.097 g, 1.34 mmol), sodium carbonate (0.191, 1.65 mmol), water (3.5
30 mL) and chloroform (3.5 mL). This stirred suspension was warmed to room

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temperature and stirred overnight. Water was added and the reaction mixture was extracted with chloroform. 2% phosphoric acid/methanol treated silica gel was added to the chloroform phase and the solvent was removed. The adsorbate was flashed on 2% phosphoric acid/methanol treated silica gel (gradient: 4:1 to 3:2 petroleum ether:ethyl acetate) to provide the title compounds as a white solid (0.464 g, 64%):
5 mp 143-144°C: NMR (DMSO-d₆); δ 9.03 (d, J = 2 Hz, 1H), 8.29 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.81 (ddd, J = 8, 1, 1 Hz, 1H), 7.78 (s, 2H), 7.63 (ddd, J = 8, 7, 1 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.52 (ddd, J = 8, 7, 1 Hz, 1H), 7.36-7.25 (m, 6H), 6.71 (d, J = 8 Hz, 1H), 5.32 (dd, J = 9, 5 Hz, 1H), 3.51-3.39 (m, 2H); MS (FAB+):
10 [M+], 3 bromine isotope pattern, 723 (20%), 725 (55%) 727 (50%) 729 (30%); Anal. Calc. for C₃₁H₂₀NBr₃O₃S: C, 51.27, H, 2.78, N, 1.93. Found: C, 51.19, H, 2.69, N, 1.86.

Example 168.

15 (R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-N-(3-nitrolo-propyl)3-phenyl-propionamide

Dicyclohexylcarbodiimide (0.605 g, 2.926 mmol) was added to a 0°C stirred solution of (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid (2.08 g, 2.926 mmol), 2-aminopropionitrile (0.215
20 mL, 2.926 mmol), HOBT (0.448 g, 2.926 mmol) in DMF (7.2 mL) under a dry nitrogen atmosphere. After 16.5 h, the reaction mixture was added to water and partitioned between water/ethyl acetate and THF. Silica gel was added to the organic phase and the solvent was removed. The adsorbate was flashed (7:3, petroleum:ethyl acetate) to provide an off-white solid (2.23 g). This solid was dissolved in
25 dichloromethane and silica gel was added. The solvent was removed and the adsorbate was flashed (gradient: dichloromethane to 97.5:2.5 dichloromethane:acetonitrile) to provide the title compound as a white solid (1.89 g, 85%): mp 194-195°C: NMR (DMSO-d₆); δ 8.70 (t, J = 6 Hz, 1 H), 8.28 (ddd, J = 8, 1, 1 Hz, 1H), 8.07 (dd, J = 8, 1 Hz, 1H), 7.80 (ddd, J = 8, 7, 1 Hz, 1H), 7.76 (s, 2H), 7.63 (ddd, J = 8, 7, 1 Hz, 1H), 7.52 (ddd, J = 8, 7, 1 Hz, 1H), 7.48 (dd, J = 8, 1, 1 Hz, 1H), 7.37-
30 J = 8, 7, 1 Hz, 1H), 7.52 (ddd, J = 8, 7, 1 Hz, 1H), 7.48 (dd, J = 8, 1, 1 Hz, 1H), 7.37-

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7.24 (m, 6H), 6.74 (d, J = 8 Hz, 1H), 5.16 (t, J = 6 Hz, 1 H), 3.51-3.26 (m, 2H), 2.62 (t, J = 6 Hz, 1 H); MS (EI): [M+], 3 bromine isotope pattern, 760, 762, 764, 766; Anal. Calc. for C₃₄H₂₃Br₃N₂O₂S: C, 53.50, H, 3.04, N, 3.67. Found: C, 53.24, H, 2.86, N, 4.02.

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Example 169.

[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetonitrile

Bromoacetonitrile (0.25 mL, 3.56 mmol) was added to a room temperature, stirred suspension of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (1.0 g, 1.78 mmol) and potassium carbonate (0.615 g, 4.45 mmol) in DMF (5 mL). After 2.5 h, the reaction mixture was added to water, filtered, washed with water and triturated with petroleum ether. The solid was dried in vacuo at 80°C to provide the title compound as a white solid (1.03 g, 96%): NMR (DMSO-d₆): δ 8.29 (d, J = 8 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 7.92 (s, 2H), 7.80 (ddd, J = 8, 7, 1 Hz, 1H), 7.65-7.51 (m, 3H), 7.27 (ddd, J = 8, 7, 1 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 5.36 (s, 2H); MS (+FAB): [M+], 3 bromine isotope pattern, 599, 601, 603, 605; Anal. Calc. for C₂₄H₁₂Br₃NOS: C, 47.87, H, 2.01, N, 2.33. Found: C, 47.83, H, 1.92, N, 2.32.

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Example 170.

(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionitrile

Trifluoroacetic anhydride (0.375, 2.65 mmol) was added to a stirred, room temperature suspension of (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionamide (1.68 g, 2.37 mmol), pyridine (0.393 mL, 4.74 mmol) and dioxane (5.4 mL). Dissolution occurred and the solution was heated in a 105°C oil bath for 2h. The reaction mixture was cooled to room temperature, diluted with ether, washed with 5% HCl and brine. Silica gel was added to the ether phase and the solvent was removed. The adsorbate was flash chromatographed (ether as eluent) to provide the title compound as a white solid (1.38

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g, 84%): mp 160-165°C: NMR (DMSO-d₆): δ 8.29 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.93 (d, J = 2 Hz, 1H), 7.91 (d, J = 2 Hz, 1H), 7.80 (ddd, 8, 7, 1 Hz, 1H), 7.65-7.33 (m, 8H), 7.23 (ddd, 8, 7, 1 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 5.87 (t, J = 7 Hz, 1H), 3.58 (m, 2H); MS (EI): [M+], 3 bromine isotope pattern, 689 (30%), 691 (95%), 693 (100%), 695 (40%); Anal. Calc. for C₃₁H₁₈Br₃NOS: C, 53.74, H, 2.62, N, 2.02. Found: C, 53.60, H, 2.60, N, 1.83.

Example 171.

5-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-1H-tetrazole

Trimethylaluminum (2.55 mL, 3.84 mmol, 2.0 M solution in toluene) was added to [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetonitrile (0.615 g, 1.02 mmol) under a dry nitrogen atmosphere. Trimethylsilyl azide (0.510 mL, 3.84 mmol) was then added and the solution was heated in a 80°C oil bath. After 16.5h the reaction mixture was cooled to room temperature and water was cautiously added. The mixture was partitioned between dilute aqueous HCl and ethyl acetate. The layers were separated and the 2% phosphoric acid in methanol washed silica gel was added to the organic phase. The solvent was removed and the adsorbate was flashed using 2% phosphoric acid in methanol washed silica gel (eluent: gradient: 4:1 to 7:3 petroleum ether:ethyl acetate) to provide the title compound as a white solid, which was recrystallized from cyclohexane (0.365g, 55%): mp 243-245°C: NMR (DMSO-d₆): δ 8.29 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 7.89 (s, 2H), 7.80 (ddd, J = 8, 7, 1 Hz, 1H), 7.66-7.57 (m, 2H), 7.55 (ddd, J = 8, 7, 1 Hz, 1H), 7.40 (ddd, J = 8, 7, 1 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 5.64 (s, 2H), 1.34 (cyclohexane, 0.3 mole eq); MS (EI): [M+], 3 bromine isotope pattern, 642, 644, 646, 648; Anal. Calc. for C₂₄H₁₃Br₃N₄OS•0.33 C₆H₁₂: C, 46.39, H, 2.55, N, 8.32. Found: C, 46.28, H, 2.43, N, 7.90.

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Example 172.

(R)-5-{1-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-2-phenyl-ethyl}-1H-tetrazole

Trimethylaluminum (7.24 mL, 14.4 mmol, 2.0 M solution in toluene) was added to (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionamide (1.33 g, 1.93 mmol) under a dry nitrogen atmosphere. Trimethylsilyl azide (1.92 mL, 14.4 mmol) was then added and the solution was heated in a 85°C oil bath. After 7h the reaction mixture was cooled to room temperature and diluted with ether. Water was cautiously added and after bubbling subsided, the mixture was partitioned between dilute aqueous HCl and ether. The ether phase was concentrated and triturated with petroleum ether, a small amount of methanol, a small amount of ether and finally petroleum ether to provide the title compound as a white solid (0.802 g, 57%): mp 238-239°C: NMR (DMSO-d₆); δ 8.28 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.81-7.74 (m, 3H), 7.62 (ddd, 8, 7, 1 Hz, 1H), 7.57-7.53 (m, 2H), 7.44 (ddd, 8, 7, 1 Hz, 1H), 7.38-7.22 (m, 5H), 6.60 (d, J = 8 Hz, 1H), 5.87 (dd, J = 9, 7 Hz, 1H), 3.90 (dd, J = 13, 7, 1H), 3.80 (dd, J = 13, 8, 1H); MS (-ESI): [M-H], 3 bromine isotope pattern, 731 (60%), 733 (90%) 735 (100%) 737 (60%); Anal. Calc. for C₃₁H₁₉Br₃N₄OS: C, 50.64, H, 2.61, N, 7.62. Found: C, 49.65, H, 2.434, N, 7.16.

Example 173.

(R)-6-Bromo-11-[3,5-dibromo-4-(1-hydroxymethyl-2-phenyl-ethoxy)-phenyl]-benzo[b]naphtho[2,3-d]thiophene

A solution of (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester (0.30 g, 0.414 mmol) in THF (4.2 mL) was added dropwise to a -78 °C, stirred solution of mixed hydride (0.435 mL, 0.414 mmol) of lithium aluminum hydride / aluminum chloride (1.0 M solution in THF) in THF (3 mL) under a dry nitrogen atmosphere over a period of 5 min. After 1 h., the solution was allowed to warm to ambient temperature. After 2 h. the reaction mixture was quenched carefully with methanol (3 mL) and further diluted

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with water (80 mL). Aqueous mixture was extracted with ethyl acetate (2 X 80 mL). The ethyl acetate extracts were washed with water, dried with brine and anhydrous MgSO₄, and concentrated to provide the title compound as a white solid (0.28 g, 97%): mp 83-85: MS (EI): [M+], 3 bromine isotope pattern, 694, 696, 698, 700.

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Example 174.

(R)-6-Bromo-11-[3,5-dibromo-4-(1-bromomethyl-2-phenyl-ethoxy)-phenyl]-benzo[b]naphtho[2,3-d]thiophene

Diethylazodicarboxylate (0.151 mL, 0.96 mmol) was added dropwise to a 0°C, stirred solution of triphenylphosphine (0.257 g, 0.98 mmol) in THF (6 mL) under a dry nitrogen atmosphere. After 20 min., lithium bromide was added to a nearly colorless reaction mixture, followed by adding a solution of (R)-6-bromo-11-[3,5-dibromo-4-(1-hydroxymethyl-2-phenyl-ethoxy)-phenyl]-benzo[b]naphtho[2,3-d]thiophene (0.273 g, 0.392 mmol) in THF (3 mL). After 1 h, the solution was allowed to warm to ambient temperature. After 2 h, the reaction mixture was quenched with water (0.2 mL) and further diluted with ethyl ether (50 mL). Silica gel (8 mL) was added. Solvent was removed and the silica adsorbate was flash chromatographed (eluent 98 : 2 petroleum ether : ethyl acetate) to provide the title compound as a white solid (0.23 g, 73%): mp > 90°C (dec.): MS (EI): [M+], 4 bromine isotope pattern, 756, 758, 760, 762, 764; Anal. Calc. for C₂₈H₁₇Br₃N₂O₃S • 0.25 hexane: C, 49.97, H, 2.97, N, 0.00. Found: C, 49.97, H, 2.83, N, 0.02.

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Example 175.

5-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-thiazolidinedione-2,4-dione

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Lithium (bis)trimethylsilylamide (1.0 M in THF, 5.32 mL, 5.32 mmol) was added dropwise over a 20 min period to a -78°C stirred solution of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (1.50 g, 2.66 mmol), 5-bromothiazolidine dione (Zask, et al., *J. Med Chem*, **1990**, 33, 1418-1423, 0.522 g, 2.66 mmol) and THF (20 mL) under a dry nitrogen atmosphere. After 45 min, the

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reaction mixture was warmed to room temperature. After 2h, the reaction mixture was added to water and acidified with 10% HCl and extracted with ether. Silica gel was added to the ether phase and the solvent was removed. The adsorbate was flashed (7:3 petroleum ether: ethyl acetate) to provide the title compound a white solid (0.882 g, 49%): NMR (DMSO-d₆); δ 12.75 (s, 1H), 8.30 (dd, J = 8, 1 Hz, 1H), 8.09 (ddd, J = 8, 1, 1 Hz, 1H), 7.92 (s, 2H), 7.81 (ddd, J = 8, 7, 1 Hz, 1H), 7.67-7.59 (m, 2H), 7.54 (ddd, J = 8, 7, 1 Hz, 1H), 7.27 (ddd, J = 8, 7, 1 Hz, 1H), 6.96 (s, 1H), 6.65 (d, J = 8 Hz, 1H); MS (-ESI): [M-H]⁻, 3 bromine isotope pattern, 674, 676, 678, 680; Anal. Calc. for C₂₅H₁₂Br₃NO₃S₂: C, 44.27, H, 1.78, N, 2.07. Found: C, 44.20, H, 1.90 , N, 2.14.

Example 176.

Phosphoric acid Di-tert-Butyl ester 2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester

Tetrazole (0.215 g, 3.0 mmol) was added in one portion to a stirred suspension of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (0.527 g, 1.0 mmol), di-tert-butyl N,N-diethylphosphoramidate (93%, 0.353 mL, 1.0 mmol) in THF at room temperature under a dry nitrogen atmosphere. Dissolution occurred. After 1h, the solution was cooled to -40°C and a suspension occurred. A solution of meta-chlorobenzoic acid (80%, 0.26 g, 1.2 mmol) was added slowly so as not to raise the temperature. The resultant suspension was slowly warmed to room temperature where dissolution occurred. Aqueous 10% sodium bisulfite was added and the biphasic mixture was stirred for 20 min. The reaction mixture was taken up in ether and washed with aqueous sodium bisulfite and saturated aqueous sodium bicarbonate. The ether phase was concentrated and filtered. The white solid was triturated with ether and then flash chromatographed (gradient: dichloromethane to 97.5:2.5 dichloromethane:acetonitrile) to provide the title compound as a white solid (0.324 g, 43%): NMR (DMSO-d₆); δ 8.25 (d, J = 9 Hz, 1H), 8.06 (d, J = 8 Hz, 1H), 7.86 (s, 2H), 7.75 (ddd, J = 8, 7, 1 Hz, 1H), 7.56 (ddd, J = 8, 7, 1 Hz, 1H), 7.50 (ddd, J = 8, 7, 1 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.14 (ddd, J = 8, 7, 1 Hz, 1H), 6.77 (d, J = 8 Hz,

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1H), 1.51 (s, 18H); MS (+FAB): [M+], 3 bromine isotope pattern, 752, 754, 756, 758; Anal. Calc. for C₃₀H₂₈Br₃O₄PS: C, 47.71, H, 3.74, N, 0.00. Found: C, 47.87, H, 3.69, N, 0.10.

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Example 177.**Phosphoric acid Mono-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl] ester**

HCl (4N in dioxane, 1.5 mL, 6 mmol) was added to a room temperature, stirred solution of phosphoric acid di-tert-butyl ester 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester (0.290 g, 0.384 mmol) in dioxane (6 mL). After 4.5 h, the solvent was removed and the solid was triturated with ether, petroleum ether and dried in vacuo to provide the title compound as a white solid (0.220, 86%): NMR (DMSO-d₆): δ 8.29 (d, J = 8 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 7.83 (s, 2H), 7.80 (ddd, J = 8, 7, 1 Hz, 1H), 7.64 (ddd, J = 8, 7, 1 Hz, 1H), 7.56-7.51 (m, 2H), 7.26 (ddd, J = 8, 7, 1 Hz, 1H), 6.71 (d, J = 8 Hz, 1H); MS (+FAB): [M+], 3 bromine isotope pattern, 640, 642, 644, 646; Anal. Calc. for C₂₂H₁₂Br₃O₄PS: C, 41.09, H, 1.88, N, 0.00. Found: C, 41.71, H, 2.22, N, 0.07.

Example 178.**2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-2-methyl-propionic acid**

Solid sodium hydroxide (0.682 g, 17.05 mmol) was added in three equal portions to a 0°C, stirred suspension of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (0.800 g, 1.421 mmol), 1,1,1-trichloro-2-methyl-2-propanol tetrahydrate (1.06 g, 4.263 mmol) in acetone (7.5 mL) over 3 h period. The resulting suspension was warmed to room temperature and stirred for 15 h. The reaction mixture was added to water, acidified with 10% aqueous HCl and extracted with ether. To the ether phase was added acid washed (2% phosphoric acid in methanol) silica gel and the solvent was removed. The adsorbate was flash chromatographed (2% phosphoric acid in methanol treated silica gel; eluent: gradient: 9:1 to 8:2 petroleum ether:ethyl acetate) to provide the title compound as an

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white solid (0.620g, 67%): mp 197-199°C: NMR (DMSO-d₆); δ 13.00 (broad s, 1H), 8.29 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 7.85 (s, 2H), 7.81 (ddd, J = 7, 6, 1 Hz, 1H), 7.67-7.60 (m, 2H), 7.52 (ddd, J = 8, 7, 1 Hz, 1H), 7.23 (ddd, J = 8, 7, 1 Hz, 1H), 6.60 (d, J = 8 Hz, 1H), 1.70 (s, 6H); MS (-ESI): [M-H], 3 bromine isotope pattern, 645 (20%), 647 (60%) 649 (1000%) 651 (30%); Anal. Calc. for C₂₆H₁₇Br₃O₃S: C, 48.10, H, 2.64, N, 0.00. Found: C, 47.78, H, 2.76, N, 0.31.

Example 179.

3-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid

β -Propiolactone (0.186 mL, 2.66 mmol) was added to a stirred, room temperature solution of 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol (1.5 g, 2.66 mmol), potassium tert-butoxide (0.314 g, 2.66 mmol) in THF (33 mL) under a dry nitrogen atmosphere. After 2 days the reaction mixture was added to water, acidified with 10% aqueous HCl and extracted with ethyl acetate. To the ethyl acetate phase was added acid washed (2% phosphoric acid in methanol) silica gel and the solvent was removed. The adsorbate was flash chromatographed (2% phosphoric acid in methanol treated silica gel; eluent: gradient: 9:1 to 8:2 petroleum ether:ethyl acetate) to provide the title compound as an off-white solid (0.748 g, 44 %): mp 218-220°C: NMR (DMSO-d₆); δ 12.48 (broad s, 1H), 8.28 (d, J = 8 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 7.83 (s, 2H), 7.79 (ddd, J = 7, 6, 1 Hz, 1H), 7.64-7.57 (m, 2H), 7.52 (ddd, J = 8, 7, 1 Hz, 1H), 7.31 (ddd, J = 8, 7, 1 Hz, 1H), 6.69 (d, J = 8 Hz, 1H), 4.44 (t, J = 6 Hz, 2H), 2.89 (t, J = 6 Hz, 2H); MS (+FAB): [M+], 3 bromine isotope pattern, 632 (30%), 634 (70%) 636 (80%) 638 (40%); Anal. Calc. for C₂₅H₁₅Br₃O₃S: C, 47.27, H, 2.38, N, 0.00. Found: C, 47.68, H, 2.36, N, 0.01.

Example 180.

(R)-3-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-butyric acid

Diethylazodicarboxylate (0.420 mL, 2.66 mmol) was added dropwise to a stirred, ambient temperature suspension of 2,6-dibromo-4-(6-bromo-benzo[b]-

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naphtho[2,3-d]thiophen-11-yl)-phenol (0.50 g, 0.89 mmol), methyl-(S)-(+)-3-hydroxybutyrate (0.30 mL, 2.66 mmol), and triphenylphosphine (0.70 g, 2.66 mmol) in benzene (6 mL) under a dry nitrogen atmosphere. Dissolution occurred and the solution was heated in an 80°C oil bath for 4.0 h. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane and silica gel (15 mL) was added. Solvents were removed and the silica adsorbate was flash chromatographed (eluent 9 : 1 petroleum ether : ethyl acetate) to provide the methyl ester as a white solid (0.345 g, 52 %): mp 143-144°C: 10 % Aqueous hydrochloride (3.0 mL) was added to a stirred solution of this methyl ester (0.308 g, 0.464 mmol) in 4.0 M hydrogen chloride / dioxane (6.0 mL) at ambient temperature. The suspension in a pressure reactor was immersed in an 80°C oil bath for 2.0 h. The solution was concentrated and ethyl ether (40 mL) was added to the resulted residue. Silica gel (3 mL) was added. Solvents were removed and the silica adsorbate was flash chromatographed (eluent: ethyl acetate) to provide the title compound as a white solid (0.143 g, 48 %): mp 175-176°C: NMR (CDCl₃); δ 8.36 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.68 (ddd, J = 8, 7, 1 Hz, 1H), 7.61-7.58 (m, 3H), 7.52 (dd, J = 8 Hz, 1H), 7.43 (ddd, J = 8, 7, 1 Hz, 1H), 7.17 (ddd, J = 8, 7, 1 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 5.29 (q, J = 7 Hz, 1H), 3.20 (dd, J = 6 Hz, 1H), 2.91 (dd, J = 6 Hz, 1H), 1.62 (d, J = 7 Hz, 3H); MS (EI): M⁺, 3 bromine isotope pattern, 646, 648, 650, 652; Anal. Calc. for C₂₆H₁₇Br₃O₃S: C, 48.10, H, 2.64, N, 0.00. Found: C, 48.49, H, 2.63, N, 0.16.

Example 181.

(R)-2-[4-(6-Hydroxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dibromo-phenoxy]-3-phenyl-propionic acid, methyl ester

To a cold (-70°C dry ice/isopropanol bath) solution of (R)-2-[4-(6-methoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dibromo-phenoxy]-3-phenyl-propionic acid, methyl ester (1.10 g, 1.63 mmol) in dry methylene chloride (11 mL) was added a 1 M solution of boron tribromide in methylene chloride (5.20 mL, 5.20 mmol, 3.2 eq) dropwise over a period of 25 minutes under a dry nitrogen atmosphere. After standing at -55°C overnight the reaction mixture was kept stirring between -20° and

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-30°C for five hours, then poured into water (50 mL) and the organics were extracted with diethyl ether (100 mL). The diethyl ether layer was washed with water and brine, concentrated, and chased with petroleum ether to the title compound as a yellow solid (1.10, 100%).

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Example 182.

(R)-2-[4-(6-Benzyloxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dibromo-phenoxy]-3-phenyl-propionic acid, methyl ester

To a solution of (R)-2-[4-(6-hydroxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dibromo-phenoxy]-3-phenyl-propionic acid, methyl ester (0.50g, 0.755 mmol) in dry N,N-dimethylformamide (5 mL) was added benzyl bromide (0.27 mL, 2.27 mmol, 3 eq) dropwise at room temperature under a dry nitrogen atmosphere. After stirring about 17 hours the reaction was quenched with water (50 mL) and the organics were extracted with ether. The extracts were washed with water, and brine and combined with silica gel. The solvent was removed and the adsorbate was flash chromatographed (97/3 petroleum ether/ethyl acetate) and the solvents chased with benzene and petroleum ether to provide the title compound as a pale yellow solid (0.572 g, 84%): NMR (CDCl₃); δ 8.30 (ddd, J = 8, 1, 1 Hz, 1H), 7.82 (ddd, J = 8, 1, 1 Hz, 1H), 7.68 (ddd, J = 8, 1, 1 Hz, 2H), 7.62 (dd, J = 3, 2 Hz, 2H), 7.60-7.55 (m, 2H), 7.51-7.26 (m, 10H), 7.16 (ddd, J = 8, 7, 1 Hz, 1H), 6.81 (ddd, J = 8, 1, 1 Hz, 1H), 5.34 (s, 2H), 5.25 (dd, J = 6, 2 Hz, 1H), 3.76 (s, 3H), 3.59 (septet, J = 7 Hz, 2H); MS (EI): [M⁺], 2 bromine isotope pattern, 750 (2%), 752 (3.5%), 754 (2.5%); Anal. Calc. for C₃₉H₂₈Br₂O₄S: C, 62.25, H, 3.75, N, 0.00; Found C, 61.66, H, 3.53, N, 0.25.

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Example 183.

(R)-2-[2,6-Dibromo-4-(6-methoxycarbonylmethoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid methyl ester

To a solution of (R)-2-[2,6-dibromo-4-(6-hydroxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid methyl ester (0.60 g, 0.906 mmol) in anhydrous N,N-dimethylformamide was added potassium carbonate (0.376 g, 2.72 mmol, 3 eq) and methylbromoacetate (0.26 mL, 2.72 mmol, 3 eq) at room

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temperature under a dry nitrogen atmosphere. After stirring for 24 hours the reaction mixture was combined with water (60 mL) the organics were extracted with diethyl ether (2x100 mL). The extracts were combined and washed with water (2x100 mL) and brine (100 mL). Silica gel was added and the solvents removed. The adsorbate
5 was twice flash chromatographed (eluent 88/12 petroleum ether/ethyl acetate and 85/15 ethyl ether/ethyl acetate) to provide the title compound as a white solid (0.493 g, 73%): NMR (CDCl₃); δ 8.38 (d, J = 8 Hz, 1H), 7.81 (d, J = Hz, 1H), 7.64-7.59 (m, 3H), 7.55 (d, J = 8 Hz, 1H), 7.48 (ddd, J = 8, 7, 1 Hz, 1H), 7.43-7.26 (m, 6H), 7.16 (ddd, J = 8, 7, 1 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 5.25 (dd, J = 8, 6 Hz, 1H), 4.94 (s,
10 2H), 3.92 (s, 3H), 3.76 (s, 3H), 3.57 (septet, J = 7 Hz, 2H); MS (EI): [M+], 2 bromine isotope pattern, 732 (1.8%), 734 (4%), 736 (0.8%); Anal. Calc. for C₃₅H₂₆Br₂O₆S, 57.24, H, 3.57, N, 0.00. Found: C, 57.01, H, 3.42, N, -0.07.

Example 184.

15 (R)-2-[4-(6-Benzyloxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-6-dibromo-phenoxy]-3-phenyl-propionic acid

To a solution of (R)-2-[4-(6-benzyloxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-6-dibromo-phenoxy]-3-phenyl-propionic acid methyl ester (0.484 g, 0.644 mmol) in tetrahydrofuran (9 mL) and methanol (3 mL) was added an aqueous solution
20 of potassium hydroxide (1N, 1.29 mL, 1.29 mmol, 2 eq) dropwise at room temperature. After stirring 2.5 hours the solvents were removed and the residue was partitioned between dilute aqueous hydrochloric acid and ether. This biphasic system was shaken vigorously and the layers were separated. The ether layer was washed with water and brine and combined with acid treated (2% phosphoric acid in
25 methanol) silica gel. The ether was removed and the adsorbate was flash chromatographed (acid treated silica gel, 90/10 petroleum ether/ethyl acetate) to provide the title compound as a white solid (0.354 g, 74.5%): [a]_D²⁵ = + 24.77° (10.091 mg/mL, CHCl₃); NMR (CDCl₃); δ 8.29 (d, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 1H), 7.68 (d, J = 8 Hz, 2H), 7.61 (dd, J = 10, 2 Hz, 2H), 7.59-7.56 (m, 1H), 7.51-7.47 (m, 3H), 7.46-7.27 (m, 8H), 7.15 (ddd, J = 8, 7, 1 Hz, 1H), 6.80 (d, J = Hz, 1H), 5.47
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(t, J = 7 Hz, 1H), 5.34 (s, 2H), 3.59 (d, J = 7 Hz, 2H); MS (CI): [(M+H)+], 2 bromine isotope pattern, 737 (6%), 739 (10%), 741 (4%); Anal. Calc. for C₃₈H₂₆Br₂O₄S: C, 61.80, H, 3.55, N, 0.00. Found: C, 62.15, H, 3.52, N, 0.07.

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Example 185.

(R)-2-[2,6-Dibromo-4-(6-carboxymethoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

To a solution of (R)-2-[2,6-dibromo-4-(6-carboxymethoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester (0.436 g, 0.594 mmol) in tetrahydrofuran (9 mL) and methanol (3 mL) was added an aqueous solution of potassium hydroxide (1N, 2.37 mL, 2.37 mmol, 4 eq) dropwise at room temperature. After stirring 3.5 hours the solvents were removed and the residue was combined with water. The suspension was acidified with 10% aqueous hydrochloric acid and diethyl ether was added. The biphasic mixture was shaken well before the layers were separated. The organic phase was washed with water and concentrated. The residue was triturated with petroleum ether and dried in vacuo to provide the title compound as a white solid (0.366 g, 87%): mp 110-120°C; [α]₂₅/D = +49.62° (10.076 mg/mL, methanol); NMR (DMSO-d₆): δ 13.21 (broad s, 2H), 8.40 (d, J = 8 Hz, 1H), 8.03 (d, J = 8 Hz, 1H), 7.74 (dd, J = 2, 8 Hz, 2H), 7.68 (ddd, J = 8, 7, 1 Hz, 1H), 7.57 (ddd, J = 8, 7, 1 Hz, 1H), 7.52 - 7.45 (m, 2H), 7.43 - 7.38 (m, 2H), 7.37 - 7.11 (m, 2H), 7.10 - 7.20 (m, 2H), 6.69 (d, J = 8 Hz, 1H), 5.30 (t, J = 7 Hz, 1H), 4.90 (s, 2H), 3.41 (d, J = 7 Hz, 2H); MS (+FAB): [M+], 2 bromine isotope pattern, 704 (9%), 706 (22%), 708 (22%); Anal. Calc. for C₃₃H₂₁Br₂O₆S: C, 56.11, H, 3.14, N, 0.00. Found: C, 55.93, H, 3.28, N, 0.09.

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Example 186.

[2,6-Dibromo-4-(6-bromo-5,5-dioxo-5H-6-benzo[b]naphtho[2,3-d]thiophen-11-yl)]-phenoxy]-acetic acid

To a stirred suspension of [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid (0.050 g, 0.0805 mmol) in glacial acetic acid (2 mL) was added a 30% aqueous solution of hydrogen peroxide (0.082 mL, 0.805

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mmol, 10 eq) dropwise at room temperature. The suspension was heated at 105-107°C for 2.5 hours. The reaction mixture was cooled to room temperature and the white solid was filtered, and washed with petroleum ether to give the title compound (0.042 g, 79%): mp 281-282.5°C; NMR (DMSO-d₆): δ 8.42 (d, J = 8Hz, 1H), 7.66-7.61 (m, 2H), 7.50 (d, J = 8Hz, 1H), 6.51-6.48 (m, 1H), 4.75 (s, 2H), 1.90 (s, 3H); MS (EI): M⁺, 3 bromine isotope pattern, 650 (32%), 652 (95%), 654 (100%), 656 (38%); Anal. Calc. for C₂₄H₁₃Br₃O₅S • CH₃COOH: C, 43.79, H, 2.40, N, 0.00. Found: C, 43.66, H, 2.26, N, 0.08.

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Example 187.

[2,6-Dibromo-4-[6-bromo-5-oxo-5H-4-benzo[b]naphtho[2,3-d]thiophen-11-yl)]-phenoxy]-acetic acid

To a stirred suspension of [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)]-phenoxy]-acetic acid (0.450 g, 0.725 mmol) in glacial acetic acid (4 mL) was added a 30% aqueous solution of hydrogen peroxide (0.75 mL, 7.25 mmol, 10 eq) dropwise at room temperature. The suspension was heated to 105°C and when dissolution did not occur an additional 15 mL of acetic acid was added. Dissolution occurred rapidly and the solution was heated at 105°C for 5.5 hours. On cooling to room temperature a yellow solid precipitated. The solid was removed and combined with the diethyl ether extracts taken from the diluted filtrate. The solid did not completely dissolve in the diethyl ether nor when ethyl acetate was added and was removed by filtration. The solid was recrystallized from acetic acid with hot filtration to the title compound as a yellow solid (0.055g, 12%): mp 287-289°C; NMR (DMSO-d₆): δ 13.3 (broad band, 1H), 8.39 (d, J = 8, 1H), 8.14 (ddd, J = 8, 1, 1 Hz, 1H), 7.91 (d, J = 2 Hz, 1H), 7.84 (ddd, J = 8, 7, 1 Hz, 1H), 7.77-7.72 (m, 2H), 7.60-7.50 (m, 3H), 6.45 (ddd, J = 8, 1, 1 Hz, 1H), 4.75 (s, 2H); MS (EI): [M⁺], 3 bromine isotope pattern, 634 (25%), 636 (70%), 638 (75%), 640 (30%); Anal. calc. for C₂₄H₁₃Br₃O₄S: C, 45.24, H, 2.06, N, 0.00. Found: C, 44.89, H, 1.76, N, 0.06.

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Example 188.

(R)-2-[2,6-Dibromo-4-(6-bromo-5,5-dioxo-5H-5(λ 6)-benzo[b]naphtho[2,3-d]-thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester

A stirred suspension of (R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester (0.94g, 1.30 mmol) in glacial acetic acid (38 mL) and a 30% solution of hydrogen peroxide (1.5 mL, 13 mmol) was heated at 100 - 110°C (dissolution occurred) for 5.5 hours and then remained at ambient temperature overnight. The solvents were removed. The solid residue was dissolved in methylene chloride and silica gel was added. The solvent was removed and the adsorbate was flash chromatographed (80 : 20 Petroleum ether : ethyl acetate) to the title compound as a yellow solid 0.937g, 95%): mp 156-157°C: [a]_D²⁵ = +47.92° (10.017 mg/mL CHCl₃); NMR (CDCl₃); δ 8.48 (d, J = 7 Hz, 1 H), 7.89 (d, J = 6 Hz, 1H), 7.74 (ddd, J = 8, 7, 1 Hz, 1 H.), 7.64 (ddd, J = 8, 7, 1 Hz, 1H), 7.54 (dd, J = 7, 4, Hz, 2H), 7.50 - 7.27 (m, 8 H), 6.44 (dd, J = 7, 1 Hz), 5.27 (dd, J = 6, 8 Hz, 1 H), 3.75 (s, 3H), 3.56 (m, 2H); MS (+FAB): [M+H]⁺, 3 Bromine pattern, 755 (8%), 757 (20%), 759 (30%), 761 (10%); Anal. Calcd. for C₃₂H₂₁Br₃O₅S: C, 50.75, H, 2.80, N, 0.00. Found: C, 50.75, H, 2.61, N, -0.04.

Example 189.

(R)-2-[2,6-Dibromo-4-(6-bromo-5,5-dioxo-5H-5(λ 6)-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid

Aqueous potassium hydroxide (1 N, 2.22 mL, 2.22 mmol) was added to a stirred solution of (R)-2-[2,6-dibromo-4-(6-bromo-5,5-dioxo-5H-5(λ 6)-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester (0.832 g, 1.11 mmol) in tetrahydrofuran (7.5 mL) / methanol (5.5 mL). After 1h the solution was concentrated, diluted with water and acidified with 10% aqueous HCl. The organics were extracted with ether. The ether was removed and the residue was dried in vacuo overnight at 53C to give the title compound as a white solid (0.534 g, 65%): mp 173-193°C: [a]_D²⁵ = +42.73°; NMR (CDCl₃); δ 8.47 (dd, J = 8, 1 Hz, 1H), 7.76 (dd, J = 8, 1 Hz, 1H), 7.74 (ddd, J = 7, 3, 1 Hz, 1H.), 7.64 (ddd, J = 7, 3, 1 Hz,

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1H), 7.55 - 7.46 (m, 3H), 7.41 - 7.27 (m, 7H), 6.42 (d, J = 8 Hz, 1H), 5.44 (t, J = 7 Hz, 1H), 3.57 (d, J = 7 Hz, 2H); MS (EI): [M+] 3 bromine pattern 740 (2%), 742 (8%), 744 (6%), 746 (2%); Anal. Calc. for: C₃₁H₁₉Br₃O₅S: C, 50.09, H, 2.58, N, 0.00. Found: C, 50.18, H, 2.71, N, 0.00.

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Example 190.**5'-Benzo[b]naphtho[2,3-d]thiophen-11-yl-[1,1':3',1'']terphenyl-2'-ol**

A solution of 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diiodo-phenol (1.26 g, 2.18 mmol), phenylboronic acid (0.584 g, 4.80 mmol), barium hydroxide octahydrate (2.75 g, 8.72 mmol), palladium acetate (10 mg, 0.087 mmol) and 6:1 dimethoxyethane:water (49 ml) was heated to 80°C overnight. An additional amount of phenylboronic acid (0.29 g, 2.40 mmol) and a catalytic amount of palladium acetate were added, and the solution was heated for four additional hours. The reaction mixture was acidified to pH 1 with conc. HCl, diluted with ethyl acetate and washed with water. The solvents were removed and the crude product was flash chromatographed (99:1 ethyl acetate: pet. ether) to provide the title compound as a white solid (0.948 g, 91%); NMR (DMSO-d₆): δ 8.76 (s, 1H), 8.61 (s, 1H), 8.05 (d, J = 8 Hz, 1H), 7.99 (d, J = 8 Hz, 1H), 7.77 (d, J = 9 Hz, 1H), 7.63-7.30 (m, 13H), 7.25 (s, 2H), 7.22 (ddd, J = 8, 8, 1 Hz, 1H), 7.08 (d, J = 9 Hz, 1H); MS (EI): 492 (100%, MI); Anal. Calc. for C₃₄H₂₂OS•1.6H₂O: C, 80.48, H, 5.01, N, 0.00. Found: C, 80.26, H, 4.63, N, 0.05.

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Example 191.**(5'-Benzo[b]naphtho[2,3-d]thiophen-11-yl)-[1,1':3',1'']terphenyl-2'-yloxy)-acetic acid**

5'-Benzo[b]naphtho[2,3-d]thiophen-11-yl-[1,1':3',1'']terphenyl-2'-ol (0.145 g, 0.30 mmol), methyl bromoacetate (0.057 mL, 0.61 mmol), potassium carbonate (0.046 g, 0.33 mmol) and N,N-dimethylformamide (5 mL) were combined and stirred at ambient temperature for 3 day. The reaction mixture was added to water and extracted with ethyl acetate. The ethyl acetate layer was washed with aqueous 1N HCl, sat. sodium bicarbonate and dried (magnesium sulfate). The ethyl acetate was removed and the crude product was flash chromatographed (95:5 ethyl acetate:

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pet. ether) to provide (5'-benzo[b]naphtho[2,3-d]thiophen-11-yl)-[1,1';3',1'']-terphenyl-2'-yloxy)-acetic acid, methyl ester as a white solid (0.177 g). Aqueous potassium hydroxide (1 N, 1.61 mL, 1.61 mmol) was added to a stirred solution of this methyl ester in 3:2 THF:methanol (5.0 mL) at ambient temperature. After 2 h the
5 solution was concentrated, diluted with water (75 mL) and acidified with 10% aqueous HCl. The solid was filtered and washed with water to provide the title compound as a white solid (0.119 g, 69%): mp >132°C (dec): NMR (DMSO-d₆): δ 12.60 (s, 1H), 8.63 (s, 1H), 8.07 (d, J = 8 Hz, 1H), 7.99 (d, J = 8 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 7.67-7.41 (m, 11H), 7.40-7.33 (m, 2H), 7.24 (ddd, J = 8, 8, 1 Hz, 1H), 6.91
10 (d, J = 9 Hz, 1H); MS (EI): 536 (100%, MI); Anal. Calc. for C₃₆H₂₄O₃S•0.5H₂O: C, 79.24, H, 4.62, N, 0.00. Found: C, 78.80, H, 4.57, N, 0.09.

Example 192.

3-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-benzyloxy-phenol

15 A suspension of 3-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol (0.390 g, 0.78 mmol) and potassium carbonate (0.108 g, 0.78 mmol) in DMF (4 mL) was stirred at 0 °C under a dry N₂ atmosphere for 20 min. Benzyl bromide (0.093 mL, 0.78 mmol) was added dropwise to this mixture over a period of ten minutes. After the mixture was stirred at 0 °C for 6.5 h., the reaction mixture was
20 quenched with aqueous hydrochloric acid to pH 1 and further diluted with water (60 mL) and aqueous mixture was extracted with methylene chloride (2 X 60 mL). The combined organic extracts were washed with water and dried with brine. Silica gel (5 mL) was added. Solvent was removed and the adsorbate was flash chromatographed (eluent: petroleum ether : methylene chloride 6:4 to petroleum ether : ethyl acetate
25 6:4) to provide a mixture (271 mg, 59%) of the title compound (87%) and 2-bromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-6-benzyloxy-phenol (13%). The mixture was used for next reaction without separation: NMR (CDCl₃): δ 8.35 (d, J = 8 Hz, 1H), 7.79 (d, J = 8 Hz, 1H), 7.72-7.33 (m, 9 H), 7.18 (d, J = 2 Hz, 1H), 7.17 (ddd, J = 8, 7, 1 Hz, 1H), 6.93 (d, J = 2 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 5.71 (s, 1H),
30 5.32 (t, J = 7 Hz, 2H).

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Example 193.**2-Bromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-6-methoxy-phenol**

Iodomethane (0.086 mL, 1.38 mmol) was added dropwise to a room
5 temperature, stirred light suspension of a mixture [3-bromo-5-(6-bromo-benzo[b]-
naphtho[2,3-d]thiophen-11-yl)-2-benzyloxy-phenol (87% pure, contaminated with
2-bromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-6-benzyloxy-phenol
(13%), 0.271 g, 0.46 mmol), potassium carbonate (0.191 g, 1.38 mmol) in DMF (2
mL) over a period of twenty minutes. After the mixture was stirred at ambient
10 temperature for 3 h., the reaction mixture was quenched with aqueous hydrochloride
to pH 1 and further diluted with water (40 mL) and aqueous mixture was extracted
with methylene chloride (80 mL). The organic extract was washed with water, dried
with brine and anhydrous MgSO₄, and concentrated to provide a mixture (279 mg,
100%) of 11-(3-methoxy-4-benzyloxy-5-bromo-phenyl)-6-bromo-benzo[b]naphtho-
15 [2,3-d]thiophene (87%) and 11-(4-methoxy-3-benzyloxy-5-bromo-phenyl)-6-bromo-
benzo[b]naphtho[2,3-d]thiophene(13%). This mixture was used for next reaction
without separation. A solution of a this mixture (279 mg, 0.49 mmol) and 10%
palladium on carbon (28 mg) in ethyl acetate: ethanol (1.5:10, 15 mL) was
hydrogenated in a Parr vessel at 51 psi at ambient temperature for 6 h. The reaction
20 mixture was filtered through a bed of Solka Floc and washed with hot ethyl acetate:
ethanol (1.5:10). Silica gel (5 mL) was added to the filtrate. Solvent was removed and
the adsorbate was flash chromatographed (eluents: petroleum ether : methylene
chloride 6:4 to petroleum ether : ethyl acetate 7:3) to provide a white solid (145 mg)
that contained about 73% 2-bromo-4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-6-
25 methoxy-phenol and 27% of the title compound. The bromine was re-introduced to
the 6 position of the majority (73 %) of the crude according to the procedures
outlined by methods in Examples 34 (acetylation of the phenol), Example 37
(bromination in the 6 position) and Example 41 (saponification of the acetyl moiety)
to provide the title compound as a white solid: mp 216-218°C; NMR (CDCl₃); δ 8.36
30 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.68-7.64 (m, 2H), 7.50-7.43 (m, 2H), 7.21

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(d, J = 2 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 6.93 (d, J = 8 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 6.20 (s, 1H), 3.86 (s, 3H); MS (+FAB): [M+], 2 bromine isotope pattern; 512.

Example 194.

5 (R)-2-[2-Bromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-6-methoxy-phenoxy]-3-phenyl-propionic acid

Prepared from 2-bromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-6-methoxy-phenol (Example 193) and (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (Example 96) according to the procedure in Example 113. White solid: mp
10 >103°C (dec.): NMR (CDCl₃); δ 8.36 (ddd, J = 8, 1, 1 Hz, 1H), 7.83 (ddd, J = 8, 7, 1 Hz, 1H), 7.67 (ddd, J = 8, 7, 1 Hz, 1H), 7.57-7.26 (m, 9H), 7.18 (ddd, J = 8, 7, 1 Hz, 1H), 6.89 (ddd, J = 8, 1, 1 Hz, 1H), 6.79 (ddd, J = 8, 7, 1 Hz, 1H), 5.29 (t, 1H), 3.76, 3.74 (ds, 3H), 3.39-3.46 (m, 2H); MS (EI): [M+], 2 bromine isotope pattern, 660; Anal. Calc. for C₃₂H₂₂Br₂O₄S: C, 58.02, H, 3.35, N, 0.00. Found: C, 58.04, H, 3.73,
15 N, 0.02.

Example 195.

3-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-methoxy-phenol

Iodomethane (0.074 mL, 1.2 mmol) was added dropwise to a rt, stirred light
20 suspension of 3-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol (0.30 g, 0.60 mmol), potassium carbonate (0.083 g, 0.6 mmol) in DMF (1.5 mL) over a period of five minutes. After the mixture was stirred at ambient temperature for 1.5 h., the reaction mixture was quenched with aqueous hydrochloric acid to pH 1 and further diluted with water (80 mL) and aqueous mixture was
25 extracted with methylene chloride (120 mL). The organic extract was washed with water and dried with brine. Silica gel (5 mL) was added. Solvent was removed and the adsorbate was flash chromatographed (eluents: petroleum ether : methylene chloride 7:3 to 1:1 and then petroleum ether : ethyl acetate 7:3) to provide the title compound as a white solid (85 mg, 29%): mp 233-234°C: NMR (CDCl₃); δ 8.35 (ddd, J = 8, 1, 1
30 Hz, 1H), 7.82 (ddd, J = 8, 1, 1 Hz, 1H), 7.66 (ddd, J = 8, 7, 1 Hz, 1H), 7.65 (dd, J = 8, 1, Hz, 1H), 7.48 (ddd, J = 8, 7, 1 Hz, 1H), 7.43 (ddd, J = 8, 7, 1 Hz, 1H), 7.17 (ddd, J

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= 8, 7, 1 Hz, 1H), 7.15 (d, J = 2 Hz, 1H), 7.00 (d, J = 2 Hz, 1H), 6.87 (ddd, J = 8, 1, 1 Hz, 1H), 5.93 (s, 1H), 4.14 (s, 3); MS (EI): [M+], 2 bromine isotope pattern, 512; Anal. Calc. for C₂₃H₁₄Br₂O₂S: C, 53.72, H, 2.74, N, 0.00. Found: C, 53.85, H, 2.98, N, 0.02.

5

Example 196.

(R)-2-[3-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-methoxy-phenoxy]-3-phenyl-propionic acid

Prepared from 3-Bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-
10 2-methoxy-phenol (Example 195) and (S)-2-hydroxy-3-phenylpropionic acid, methyl
ester (Example 96) according to the procedure in Example 113. White solid: mp
>99°C (dec.): NMR (CDCl₃); δ 8.34 (ddd, J = 8, 1, 1 Hz, 1H), 7.79 (ddd, J = 8, 7, 1
Hz, 1H), 7.64 (ddd, J = 8, 7, 1 Hz, 1H), 7.52 (dd, J = 8, 1, Hz, 1H), 7.45 (ddd, J = 8, 7,
1 Hz, 1H), 7.39 (ddd, J = 8, 7, 1 Hz, 1H), 7.28-7.07 (m, 7H), 6.67 (ddd, J = 8, 7, 1 Hz,
15 1H), 6.63 (d, J = 2 Hz, 1H), 4.91-4.84 (m, 1H), 3.33-3.20 (m, 2H), 3.95, 3.89 (ds,
3H); MS (+FAB): [M+H]⁺, 2 bromine isotope pattern, 660, 662, 664; Anal. Calc. for
C₃₂H₂₂Br₂O₄S: C, 58.02, H, 3.35, N, 0.00. Found: C, 58.37, H, 3.63, N, 0.03.

Example 197.

20 2,4-Difluoro-3-methoxy-benzoic acid

A solution of 5-bromo-1,3-difluoro-2-methoxy-benzene (12.35g, 55.4 mmole,
L. I. Kruse, et al., *Biochemistry* **1986**, *25*, 7271-7278) in anhydrous tetrahydrofuran
(350 mL) was transferred via cannula into a 1L flask which had been flame dried. The
solution was cooled to -80°C and a solution of n-butyl lithium (2.5 M in hexanes,
25 24.35 mL, 60.9 mmol) was added dropwise via syringe pump over a 1 hour period
with stirring under a dry nitrogen atmosphere. After stirring 2.5 hours, dry carbon
dioxide gas was bubbled into the cold reaction mixture for 0.5 hour. The solution was
then poured onto crushed dry ice and stirred for 0.5 hours. The mixture was
causiously added to water (600mL) and acidified with 10% HCl. The organics were
30 extracted with ether. The extracts were combined and washed with brine. After
concentrating and standing at room temperature for two days the residue was

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redissolved in ether and combined with acid treated (2% H₃PO₄ in methanol) silica gel. The solvent was removed and the adsorbate was flash chromatographed to give the title compound as an off-white solid: mp 191-192°C: NMR (400MHz, DMSO-d₆); δ 13.37 (broad singlet, 1H), 7.63-7.58 (m, 1H), 7.25 - 7.20 (m, 1H), 3.92(s, 3H);
5 MS (+ FAB): (M + H): 189 (12%), 154 (100%), 136 (75%); Anal. Calc. for C₈H₆F₂O₃: C, 51.08; H, 3.21. Found: C, 50.98, H, 3.15.

Concentration of less polar fractions gave 6-bromo-2,4-difluoro-3-methoxy-benzoic acid (3.44g, 23%) as a white solid: mp 92-94°C: NMR (400MHz, DMSO-d₆); δ 14.18 (broad singlet, 1H), 7.65 (dd, J = 3, 1 Hz, 1H), 3.94 (s, 3H); MS: (+FAB) (M + H):
10 267/269 (38%), 91 (100%); Anal. calc. for C₈H₅BrF₂O₃: C, 35.98, H, 1.89, N, 0.00. Found: C, 36.26, H, 1.79, N 0.03.

Example 198

(2-Benzyl-benzo[b]thiophen-3-yl)-(2-4-difluoro-3-methoxy-phenyl)-methanone

15 To a suspension of 2,4-difluoro-3-methoxy-benzoic acid (3.55g., 18.9 mmol) and N,N-dimethylformamide (3 drops) in anhydrous methylene chloride (70 mL) was added oxalyl chloride (2.80 mL, 32.1 mmol) dropwise under a dry nitrogen atmosphere. After stirring 3 hours additional oxalyl chloride (1.6 mL, 16.1 mmol) was added. After stirring another hour the solvents and excess oxalyl chloride were
20 removed to give a semi-solid residue which was used in the following reaction.

To a thick suspension of 2 benzylbenzo[b]thiophene (3.85g, 17.2 mmole) and the above acid chloride (3.90g, 18.9 mmole) in methylene chloride (56 mL) cooled to -80°C was added tin IV chloride (4.43 mL, 37.8 mmol) dropwise over a period of 55 minutes under a dry nitrogen atmosphere. After stirring for an additional hour the ice-
25 bath was removed. Dissolution occurred as the solution warmed to room temperature. After stirring ca. 15 hours the reaction mixture was added to water (200 mL) and the organics were extracted with ether. The extracts were combined, washed with brine and combined with silica gel. The solvents were removed and the adsorbate was flash chromatographed (gradient 100% petroleum ether to 97 / 3 petroleum ether / ethyl
30 acetate) to give the title compound as a yellow oil (2.19g, 34% yield): NMR (400

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MHz, DMSO-d₆): δ 7.97-7.94 (m, 1H), 7.77-7.20 (m, 10H), 4.33 (s, 2H), 4.24 (s, 3H); MS (EI) (M⁺): 394 (100%).

Example 199.**5 3-(Benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6 difluoro-phenol**

To a cold (-78°C) solution of (2-benzyl-benzo[b]thiophen-3-yl)-(2-4-difluoro-3-methoxy-phenyl)-methanone (2.07g, 5.28 mmole) in anhydrous methylene chloride (20 mL) was added boron tribromide (1.60 mL, 16.9 mmol) dropwise via syringe pump over a period of 43 minutes under a dry nitrogen atmosphere. After stirring an additional 14 minutes the ice bath was removed and the reaction was allowed to stir at room temperature for about 4 hours. The dark red mixture was cooled in an ice bath and cautiously quenched with water and the organics were extracted with ether. The extract was washed with brine and concentrated to give the crude product as a yellow foam (2.2 g). The solid was redissolved in a mixture of ether, tetrahydrofuran, and methylene chloride and combined with silica gel (60 mL). The solvents were removed and the adsorbate was flash chromatographed (90/10 petroleum ether / ethyl acetate) to give the title compound as a white solid (1.4g, 74%): NMR (300 MHz, DMSO-d₆); δ 10.57 (s, 1H), 8.69 (s, 1H), 8.09 (d, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 7.64-7.23 (m, 6H), 6.94-6.83 (m, 2H).

20

Example 200.**3-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6 difluoro-phenol**

To a cold (-23°C dry ice / carbon tetrachloride bath) stirred solution of 3-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6 difluoro-phenol (1.38 g, 3.81 mmol) in methylene chloride (35 mL) was added a solution of bromine (0.22 mL, 4.19 mmol) in methylene chloride (7 mL) dropwise, very slowly, over a period of 28 minutes. After stirring an additional 1.5 h the reaction was quenched with dilute sodium bisulfite and the organics were extracted with ether. The extract was concentrated to give a yellow solid (1.64 g, 98% crude yield). A small portion was taken up in methylene chloride and combined with silica gel. The solvent was removed and the adsorbate was flash chromatographed (85/15 petroleum ether / ethyl acetate) to give

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the title compound as an off white solid: mp 180-182°C; NMR (400 MHz, DMSO-d₆); δ 10.64 (s, 1H), 8.30 (d, J = 9 Hz, 1H), 8.09 (d, J = 9 Hz, 1H), 7.82-7.78 (m, 1H), 7.64-7.51 (m, 3H), 7.42-7.37 (m, 1H), 7.33-7.29 (m, 1H), 6.96-6.91 (m, 1H), 6.81-6.78 (m, 1H); MS (FAB): (M-H): one bromine pattern observed; 439 / 441 (8%);

5 Anal. Calc. for C₂₂H₁₁BrF₂OS: C, 59.88, H, 2.51, N, 0.00%. Found: C, 59.82, H, 2.59, N, 0.06.

Example 201.

[3-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenoxy]-acetic acid

10 To a suspension 3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6 difluoro-phenol (0.200 g, 0.453 mmol) and potassium carbonate (0.085, 0.612 mmol) in N,N-dimethylformamide (2 mL) was added methyl bromoacetate (0.086 mL, 0.906 mmol) dropwise at room temperature under a dry nitrogen atmosphere. After stirring

15 2.5 hours the reaction mixture was combined with water (50 mL) and the organics were extracted with ether. The extract was combined with silica gel, the solvent was removed and the adsorbate was flash chromatographed (90/10 petroleum ether / ethyl acetate). The solvents were chased with benzene (2x) and petroleum ether to give [3-(6-bromo-benzo[b]naphtho[2, 3-d]thiophen-11-yl)-2, 6-difluoro-phenoxy]-acetic acid, methyl ester as a white solid (0.198 g, 85%). To a solution of this methyl ester (0.190

20 g, 0.370 mmol) in tetrahydrofuran (3 mL) and methanol (1 mL) was added a 1N aqueous solution of potassium hydroxide (0.55 mL, 0.55 mmol) dropwise at room temperature. After stirring 1 hour the solvents were removed and water was added to the solid residue. The aqueous mixture was acidified with 10% HCl and the organics were extracted with ether. After several minutes of vigorous shaking the layers were

25 separated and the organic layer was washed with water and concentrated. The residue was chased with benzene and dried in vacuo to give the title compound as a white solid (0.177g, 95%): mp 195-197°C: NMR (400 MHz, DMSO-d₆): δ 13.11 (broad s, 1H), 8.31 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 7.83-7.79 (m, 1H), 7.64-7.46 (m, 4H), 7.31-7.27 (m, 1H), 7.23-7.17 (m, 1H), 6.81 (d, J = 8 Hz, 1H), 4.89 (s, 2H); MS(-

30 FAB): (M-H): one bromine pattern observed: 497/499 (35%/38%); HRMS: Calc. for

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C₂₄H₁₃BrF₂O₃S M⁺: 497.97368, measured mass: 497.97787, mass deviation 4.19 mmu; Anal. HPLC 97% pure; Anal. Calc. for C₂₄H₁₃BrF₂O₃S: C, 57.72, H, 2.62% N, 0.00. Found: C, 56.77, H, 2.79% N, 0.00.

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Example 202.

(R)-2-[3-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenoxy]-propionic acid

To a solution of 3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenol (0.570 g, 1.29 mmol), commercially available (S)-lactic acid, methyl ester. (0.246 mL, 2.58 mmol) and triphenylphosphine (0.677g, 2.58 mmol) in dry benzene (7 mL) was added diethylazodicarboxylate (0.406 mL, 2.58 mmol) dropwise at room temperature under a dry nitrogen atmosphere. The reaction mixture was sealed in a pressure bottle and immersed in a pre-heated oil bath at 105°C. After heating for 2.5 hours the mixture was stirred at ambient temperature for about 14 hours. The reaction mixture was then diluted with methylene chloride and combined with silica gel. The solvents were removed and the adsorbate was flash chromatographed (90/10 petroleum ether / ethyl acetate) to give (R)-2-[3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenoxy]-propionic acid, methyl ester as a white solid (0.59 g, 86%). To a solution of this methyl ester (0.46 g, 0.929 mmol) in tetrahydrofuran (18 mL) and methanol (6 mL) was added a 1N aqueous solution of potassium hydroxide (1.39 mL, 1.39 mmol) dropwise at room temperature. After stirring for 2 hours the solvents were removed and the residue was combined with water (50 mL) and acidified with 10% HCl. The solid was extracted into ether. The layers were shaken together well, separated, and the organic layer was washed with water and concentrated to give the title compound as a white solid (0.396 g, 88%): [α]_D²⁵ = +13.22 (9.383 mg/mL methanol); NMR (400 MHz, DMSO-d₆): δ 13.11 (s, 1H), 8.31 (d, J = 8 Hz, 1H), 8.10-8.08 (m, 1H), 7.83-7.78 (m, 1H), 7.65-7.46 (m, 4H), 7.32-7.19 (m, 2H), 6.82-6.75 (m, 1H), 4.98-4.93 (m, 1H), 1.53-1.50 (m, 3H); MS (-FAB): (M-H): one bromine pattern observed: 511 / 513 (2%); Anal. Calc. for C₂₅H₁₅BrF₂O₃S: C, 58.49, H, 2.95, N, 0.00. Found: C, 58.41, H, 3.44, N, 0.02.

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Example 203.**(R)-2-[3-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenoxy]-3-phenyl-propionic acid**

To a solution of 3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenol (0.700, 1.59 mmol), (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (0.572g, 3.17mmol) and triphenylphosphine (0.831g, 3.17 mmol) in dry benzene (10 mL) was added diethylazodicarboxylate (0.50 mL, 3.17mmol) dropwise at room temperature under a dry nitrogen atmosphere. The reaction mixture was sealed in a pressure bottle and immersed in a pre-heated oil bath at 105°C and heated for 2.5 hours. After stirring at ambient temperature for 14 hours the reaction mixture was diluted with methylene chloride and combined with silica gel. The solvents were removed and the adsorbate was flash chromatographed (90/10 petroleum ether / ethyl acetate) to give (R)-2-[3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenoxy]-3-phenyl-propionic acid, methyl ester as an off white solid (0.73g., 76%). To a solution of this methyl ester (0.66g, 1.09 mmol) in tetrahydrofuran (21mL) and methanol (7 mL) was added a 1N aqueous solution of potassium hydroxide (1.64mL, 1.64mmol). After stirring for two hours the solvents were removed and the residue was combined with water (50 mL) and acidified with 10% HCl. The solid was extracted into ether and the layers were shaken well together for several minutes before they were separated. The organic layer was washed with water and concentrated to give the title compound as a white solid (0.613g, 95%): [a]_D²⁵ = -13.81 (9.413 mg/mL chloroform); NMR (400MHz, DMSO-d₆): δ 13.21 (s, 1H), 8.30 (d, J = 8 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 7.82 - 7.78 (m, 1H), 7.62 - 7.41 (m, 4H), 7.35 - 7.14 (m, 7H), 6.74 (dd, J = 8, 9 Hz, 1H), 5.17 - 5.11 (m, 1H), 3.32 - 3.24 (m, 1H), 3.19 - 3.12(m, 1H), NMR indicates that 0.22 mole eq. of benzene is present; MS (+FAB): (M:⁺): one bromine pattern observed, 588 / 590 (78%, 75%); Anal. Calc. for C₃₁H₁₉BrF₂O₃S·0.22 C₆H₆: C, 63.99, H, 3.38, N, 0.00. Found: C, 64.52, H, 3.48, N, 0.06.

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Example 204.**2-Benzofuranylphenyl-methanone**

According to the procedure in *Syn. Comm.* **1987**, 17, 341-354, salicylaldehyde (21.3 mL, 0.20 mol), 2-bromoacetophenone (39.8 g, 0.20 mol), potassium carbonate (30%, 300 g in 700 mL water), tetrabutylammonium sulfate (3.5 g, 5 mol%) and dichloromethane (1.5 L) were stirred vigorously for 19 h. The layers were separated, the dichloromethane phase was washed with water and brine. It was then concentrated and the residue was recrystallized from ethanol (200 mL) to provide the title compound as white crystals (37.9 g, 85%): mp 88-90°C: NMR (DMSO-d₆): δ 8.00 (m, 2H), 7.86 (ddd, J = 8, 1.5, 0.5 Hz, 1H), 7.80 (d, J = 1 Hz, 1H), 7.77 (ddd, J = 8, 2, 1 Hz, 1H), 7.77 (ddd, J = 8, 2, 1 Hz, 1H), 7.72 (m, 1H), 7.63-7.55 (m, 3H), 6.73 (dd, J = 8, 1 Hz, 1H), 7.39 (ddd, J = 8, 7, 1 Hz, 1H); MS (EI): [M⁺], 222 (100%); Anal. Calc. for C₁₅H₁₀O₂: C, 81.07, H, 4.54, N, 0.00. Found: C, 81.05, H, 4.44, N, -0.09.

Example 205.**2-Benzyl-benzofuran**

A suspension of 2-benzofuranylphenyl-methanone (34.8 g, 0.157 mol), hydrazine monohydrate (31 mL, 0.639 mol) and diethylene glycol (72 mL) was heated to reflux for 10 min and cooled to room temperature. Potassium hydroxide (22.9 g, 0.408 mol) was added. The reaction mixture was heated in 130°C oil bath for 1 h., cooled to room temperature and added to water. The oil was extracted with ether. Silica ge was added to the ether phase and the solvent was removed. The adsorbate was flash chromatographed eluent: (petroleum ether) to provide the title compound as an oil (23.9 g, 90%): NMR (CDCl₃): δ 7.5-7.1 (m, 9H), 6.38 (s, 1H), 4.10 (s, 2H).

Example 206.**(2-Benzyl-benzofuran-3-yl)-(4-methoxy-phenyl)-methanone**

Tin tetrachloride (6.5 mL, 55.5 mmol) was added dropwise over a 30 minute period to a stirred solution of 2-benzyl-benzofuran (10.0 g, 48.01 mmol), anisoyl chloride (8.51 g, 49.93 mmol) and carbon disulfide (53 mL) at room temperature under a dry nitrogen atmosphere. After 15 h the reaction mixture was added to water

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and extracted with dichloromethane. Silica gel was added to the dichloromethane phase and the solvent was removed. The adsorbate was flash chromatographed (95:5 petroleum ether:ethyl acetate as eluent) to provide the title compound as a white solid (13.84 g, 84%): mp 84-85°C: NMR (CDCl₃); δ 7.87 (dm, J = 9 Hz, 2H), 7.46 (dm, 1H), 7.36-7.12 (m, 8H), 6.97 (dm, J = 9 Hz, 2H), 4.29 (s, 2H), 3.90 (s, 3H): MS (EI): 342 (100%, MI); Anal. Calc. for C₂₃H₁₈O₃: C, 80.68, H, 5.30, N, 0.00. Found: C, 80.61, H, 5.25, N, 0.10.

Example 207.

10 (2-Benzyl-benzofuran-3-yl)-(2, 4-dimethoxy-phenyl)-methanone

Prepared from 2-benzyl-benzofuran and 2, 4-dimethoxybenzoyl chloride according to the procedure in Example 207. White solid (6.88g): mp 74-76°C; NMR (CDCl₃); δ 7.47(d, J = 8Hz, 1H), 7.40 (dd, J = 2,1 Hz, 1H), 7.31 - 7.24 (m, 5H), 7.24 - 7.19 (m, 2H), 7.16 - 7.12 (m, 1H), 6.55 (d, J = 2, Hz, 1H), 6.48 (s, 1H), 4.29 (s, 2H), 3.89 (s, 3H), 3.58 (s, 3H), MS (EI): [M⁺ + m/z] 372(55%), 165(100%), 234(88%), Anal. Calc. for C₂₄H₂₀O₄, C,77.40, H, 5.41, N, 0.00. Found: C, 77.48, H, 5.44, N, 0.09.

Example 208.

20 4-Benzo[b]naphtho[2,3-d]furan-11yl)-phenol

Boron tribromide (1.0 M in dichloromethane, 130 mL, 130 mmol) was added dropwise over a 30 minute period to a stirred, -78°C solution of (2-benzyl-benzofuran-3-yl)-(4-methoxy-phenyl)-methanone (12.0 g, 35.05 mmol) in dichloromethane (140 mL) under a dry nitrogen atmosphere. The solution was warmed to room temperature. After 23 h, water was cautiously added. The layers were separated and the dichloromethane layer was washed with water (3X), brine and silica gel was added to it. The solvent was removed and the adsorbate was flash chromatographed (gradient: 9:1 to 1:1 petroleum ether :ethyl acetate) to provide the title compound as an off-white solid (4.56 g, 42%): mp 137-138°C: NMR (CDCl₃); δ 8.01 (dt, J = 8 Hz, 1H), 7.94 (s, 1H), 7.89 (dm, J = 8 Hz, 1H), 7.53 (m, 2H), 7.44-7.36 (m, 2H), 7.38 (d, J = 9 Hz, 2H), 7.10 (d, J = 9 Hz, 2H), 7.13-7.06 (m, 1H), 7.01 (dm, J = 8 Hz, 1H); MS

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(EI): 310 (100%, MI); High Resolution MS (EI) Calc. for C₂₂H₁₄O₂: 310.0993803, Found: 310.09878; Anal. Calc. for C₂₂H₁₄O₂: C, 85.14, H, 4.55, N, 0.00. Found: C, 84.33, H, 4.30, N, 0.03.

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Example 209.**4-(Benzo[b]naphtho[2,3-d]furan-11-yl)-benzene-1,3-diol**

To a cold (-76°C dry ice, isopropanol bath) solution of (2-benzyl-benzofuran-3-yl)-(2,4-dimethoxy-phenyl)-methanone (6.13 g, 16.5 mmol) in anhydrous methylene chloride (60 mL) was added a 1 M solution of boron tribromide in methylene chloride (100 mL, 100 mmol, 6.06 eq) dropwise over a period of 20 minutes under a dry nitrogen atmosphere. The dry ice bath was removed and the reaction mixture was stirred at ambient temperature for 45 hours. After cooling in an ice bath water was carefully added and after quenching the reaction mixture was further diluted with water (300 mL). The organics were extracted with diethyl ether and methylene chloride. The extracts were combined, washed with water and brine, and combined with silica gel. The solvents were removed and the adsorbate was flash chromatographed (80/20 petroleum ether/ethyl acetate) to provide the title compound as a white solid (2.07 g, 38%): mp 201-202°C; NMR (CDCl₃); δ 8.03 (ddd, J = 8, 7, 1 Hz, 1H), 8.01 (s, 1H), 7.82 - 7.79 (m, 1H), 7.58 - 7.54 (m, 2H), 7.48 - 7.43 (m, 2H), 7.20 (d, J = 8 Hz, 1H), 7.18 - 7.15 (m, 2H), 6.70 (m, 2H), 5.00 (s, 1H), 4.70 (s, 1H); Hi Res MS, Calc. Sample Mass for C₂₂H₁₄O₃, 326.0942951, Measured Mass 326.09019, mass deviation 4 mmu. Anal. Calc. for C₂₂H₁₄O₃: C, 80.97, H, 4.32, N, 0.00. Found: C, 79.80, H, 4.10, N, 0.07.

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Example 210.**2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-phenol**

A stirred suspension of 4-benzo[b]naphtho[2,3-d]furan-11-yl-phenol (3.0 g, 9.67 mmol) in acetic acid (85 mL) and water (6 mL) was heated slightly to effect dissolution. Bromine (1.8 mL, 34.01 mmol) in acetic acid (20 mL) was then added dropwise over a 10 minute period. The resultant suspension was stirred at room temperature for 2 h. Water and solid sodium thiosulfite were added and the reaction

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mixture was filtered. The solid was washed with water and triturated with petroleum ether to provide a white solid (4.37 g, 83 %). A portion (1.0 g) of this solid was recrystallized from acetic acid (45 mL) and then hexane to provide the title compound as a white solid: mp 175-176°C; NMR (CDCl₃); δ 8.45 (ddd, J = 8, 1, 1 Hz, 1H), 7.74 (ddd, J = 8, 1, 1 Hz, 1H), 7.70-7.65 (m, 2H), 7.62 (s, 2H), 7.53-7.48 (m, 2H), 7.20 (ddd, J = 8, 7, 1 Hz, 1H), 7.02 (ddd, J = 8, 1, 1 Hz, 1H), 6.17 (s, 1H); MS (EI): [M+], 3 bromine isotope pattern, 544 (30%), 546 (100%), 548 (100%) 550 (30%); Anal. Calc. for C₂₂H₁₁Br₃O₂: C, 48.30, H, 2.03, N, 0.00. Found: C, 48.22, H, 1.79, N, 0.11.

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Example 211.**2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-3-hydroxy-phenol**

To a solution of the 4-(benzo[b]naphtho[2,3-d]furan-11-yl)-benzene-1,3-diol (1.48g, 4.55 mmole) and acetic acid potassium salt (4.46g, 45.5 mmole) in glacial acetic acid (15 mL) was added bromine (0.75 mL, 14.6 mmole) dropwise over a period of 20 minutes at room temperature. After stirring 0.5 hours the mixture was concentrated and the residue was diluted with water (20mL). The resulting solid was filtered, washed with water and petroleum ether and dried in vacuo at 40°C to give the crude product (2.5g). The solid was taken up in ethyl acetate, combined with silica gel and the solvent was removed. The adsorbate was flash chromatographed (gradient 85/15 petroleum ether / ethyl acetate) to give a yellow solid (0.990g, mixture of di and tri brominated products). To a cold (-10°C,) solution of this solid (0.437 g, 1.11 mmol) in anhydrous methylene chloride (10 mL) was added a solution of bromine (0.057 mL, 1.11 mmol) in anhydrous methylene chloride (2 mL) dropwise over a period of 30 minutes under nitrogen. After stirring in the warming bath overnight the reaction mixture was poured into water (80 mL) and extracted with diethyl ether. The extracts were combined, washed well with a dilute aqueous solution of sodium bisulfite and brine and silica gel was added. The solvents were removed and the adsorbate was flash chromatographed (87/13 petroleum ether/ethyl acetate) to give the title compound as an off-white solid (0.429 g): mp 226-228°C; NMR (CDCl₃); δ

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8.48 (ddd, J = 8, 1, 1 Hz, 1H), 7.73-7.69 (m, 2H), 7.66 (ddd, J = 8, 1, 1 Hz, 1H), 7.51 (ddd, J = 8, 1, 1 Hz, 2H), 7.49 (s, 1H), 7.22 (ddd, J = 8, 7, 1 Hz, 1H), 7.04 (ddd, J = 8, 1, 1 Hz, 1H), 6.18 (s, 1H), 5.47 (s, 1H); MS (EI): [M+], 3 bromine isotope pattern, 560 (20%), 562 (75%), 564 (44%), 566 (25%); Anal. Calc. for C₂₂H₁₁Br₃O₃: C, 46.93, H, 1.97, N, 0.00. Found: C, 46.63, H, 1.93, N, 0.09.

Example 212.

4-(Benzo[b]naphtho[2,3-d]furan-11-yl-phenoxy)-acetic acid methyl ester

Methyl bromoacetate (0.554 mL, 5.8 mmol) was added to a stirred, room temperature suspension of 4-benzo[b]naphtho[2,3-d]furan-11-yl-phenol (0.90 g, 2.90 mmol), potassium carbonate (0.81 g, 5.8 mmol) and dimethylformamide (7 mL). After 20 h, the reaction mixture was added to water and extracted with ether. Silica gel was added to the ether phase and the solvent was removed. The adsorbate was flash chromatographed (9:1 petroleum ether: ethyl acetate as eluent) to provide the title compound as a white solid (0.845 g, 76%): mp 146-147°C: NMR (DMSO-d₆); δ 8.19 (s, 1H) 8.13 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 7.67 (d, J = 8 Hz, 1H), 7.58 (ddd, J = 8, 7, 1 Hz, 1H), 7.50 (ddd, J = 8, 7, 1 Hz, 1H), 7.47-7.43 (m, 1H), 7.43 (d, J = 9 Hz, 2H), 7.24 (d, J = 9 Hz, 2H), 7.17 (ddd, J = 8, 7, 1 Hz, 1H), 6.88 (dd, J = 8, 5 Hz, 1H), 4.98 (s, 2H), 3.76 (s, 3H); MS (EI): 382 (100%, M⁺); Anal. Calc. for C₂₅H₁₈O₄: C, 78.52, H, 4.74, N, 0.00. Found: C, 77.88, H, 4.71, N, 0.07.

Example 213.

4-(Benzo[b]naphtho[2,3-d]furan-11-yl-phenoxy)-acetic acid

Potassium hydroxide (1.0 M, 2.85 mL, 2.85 mmol) was added to a stirred solution of 4-(benzo[b]naphtho[2,3-d]furan-11-yl-phenoxy)-acetic acid methyl ester (0.80 g, 2.09 mmol) in THF (9 mL) and methanol (9 mL). After 2 h, the solvents were removed, water was added and the reaction mixture was acidified with 10% HCl. After stirring overnight, the solid was filtered and washed with water, triturated with hexane and dried in vacuo at 100°C to provide a white solid (0.735 g, 95%). This solid was recrystallized from acetic acid and then hexane/ethyl acetate to provide the title compound as a white solid (0.338 g, 44%): mp 205-207°C: NMR (CDCl₃); δ

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8.01 (d, J = 8, 1, 0.5 Hz, 1H), 7.95 (s, 1H), 7.76 (ddd, J = 8, 1, 0.5 Hz, 1H), 7.55-7.36 (m, 4H), 7.47 (d, J = 9 Hz, 2H), 7.21 (d, J = 9 Hz, 2H), 7.08 (ddd, J = 9, 8, 1 Hz, 1H), 6.88 (ddd, J = 8, 1, .5 Hz, 1H), 4.89 (s, 2H); MS (EI): 368 (100%, MI); High Resolution MS (EI) Calc. for C₂₄H₁₆O₄: 368.10486 Found: 368.10867. Anal. Calc. for C₂₄H₁₆O₄: C, 78.25, H, 4.38, N, 0.00. Found: C, 77.84, H, 4.30, N, 0.14.

Example 214.

[2, 6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan -11-yl)-phenoxy]-acetic acid methyl ester

10 Methyl bromoacetate (.554 mL, 5.8 mmol) was added to a stirred, room temperature suspension of 2, 6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-phenol (1.6 g, 2.92 mmol), potassium carbonate (0.81 g, 5.8 mmol) and dimethylformamide (7 mL). After 21 h, the reaction mixture was added to water and filtered. The solid was taken up in THF and silica gel was added. The solvent was removed. The adsorbate was flash chromatographed (9:1 petroleum ether: ethyl acetate as eluent) to provide the title compound as a white solid (0.987 g, 55%): mp 188-189°C: NMR (DMSO-d₆); δ 8.37 (d, J = 8 Hz, 1H), 7.91 (s, 2H), 7.84 (d, J = 8 Hz, 1H), 7.80 (ddd, J = 8, 7, 1 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.64-7.58 (m, 2H), 7.31 (t, J = 8 Hz, 1H), 6.92 (d, J = 8, 1H), 4.88 (s, 2H), 3.80 (s, 3H); MS (EI): [M+], 3 bromine isotope pattern, 616 (30%), 618 (100%) 620 (100%) 622 (30%); Anal. Calc. for C₂₅H₁₅Br₃O₄: C, 48.50, H, 2.44, N, 0.00. Found: C, 48.53, H, 2.29, N, 0.00.

Example 215.

[2, 6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan -11-yl)-phenoxy]-acetic acid

25 Potassium hydroxide (1.0 M, 1.60 mL, 1.60 mmol) was added to a stirred solution of [2, 6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-phenoxy]-acetic acid methyl ester (0.90 g, 1.45 mmol) in THF (9 mL) and methanol (5 mL). After 3 h, the solvent was removed, water was added and the reaction mixture was acidified with 10% HCl. After stirring overnight, the solid was filtered and washed with water, triturated with hexane and dried in vacuo at 100°C to provide the title compound as a white solid (0.821 g, 94%): mp 250-252°C: NMR (DMSO-d₆); δ 8.37

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(d, J = 8 Hz, 1H), 7.90 (s, 2H), 7.84 (d, J = 8 Hz, 1H), 7.70 (ddd, J = 8, 6, 1 Hz, 1H), 7.61 (ddd, J = 8, 1, 1 Hz, 1H), 7.62-7.58 (m, 2H), 7.31 (ddd, J = 8, 7, 1 Hz, 1H), 6.92 (ddd, J = 8, 1, 1 Hz, 1H), 4.75 (s, 2H); MS (EI): [M+], 3 bromine isotope pattern, 602 (40%), 604 (95%), 606 (100%), 608 (40%); Anal. Calc. for C₂₄H₁₃Br₃O₄: C, 47.64, H, 2.17, N, 0.00. Found: C, 47.33, H, 1.95, N, 0.04.

Example 216.

(R)-2-[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-phenoxy]-3-phenyl-propionic acid

10 Diethylazodicarboxylate (DEAD, 0.108 mL, 0.686 mmol) was added to a stirred, room temperature solution of 2, 6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11yl)-phenol (0.250 g, 0.457 mmol), (S)-2-hydroxy-3-phenylpropionic acid, methyl ester (0.124 g, 0.686 mmol), triphenylphosphine (0.180 g, 0.686 mmol) and benzene (2 mL) under a dry nitrogen atmosphere. Dissolution occurred and the
15 solution was heated in an 80°C oil bath for 4.5 h. Upon cooling to room temperature, the reaction mixture was diluted with ether and silica gel was added. The reaction mixture was concentrated and the silica adsorbate was flash chromatographed (95 : 5 petroleum ether : ethyl acetate) to provide a white solid (0.266 g, 82%). Aqueous potassium hydroxide (1 N, 1.3 mL, 1.3 mmol) was added to a stirred solution of this
20 oil in THF (3 mL)/methanol (1.3 mL). After 1.5h the solution was concentrated, diluted with water (100 mL) and acidified with 10% aqueous HCl. The solid was filtered, washed with water and triturated with petroleum ether to provide the title compound as a white solid (0.256 g, 98%): NMR (DMSO-d₆); 13.25 (broad s, 1H), 8.36 (d, J = 8 Hz, 1H), 7.84-7.77 (m, 3H), 7.67-7.56 (m, 3H), 7.40 (d, J = 8 Hz, 2H),
25 7.33 (t, J = 8 Hz, 2H), 7.27 (t, J = 8 Hz, 2H), 6.85 (ddd, J = 8, 1, 1 Hz, 1H), 5.31 (t, J = 7 Hz, 1H), 3.41 (d, J = 7 Hz, 2H); MS (+FAB): [M+], 3 bromine isotope pattern, 692 (35%), 694 (90%), 696 (100%), 698(50%); Anal. Calc. for C₃₁H₁₉Br₃O₄: C, 53.56, H, 2.75, N, 0.00. Found: C, 52.44, H, 2.82, N, -0.13.

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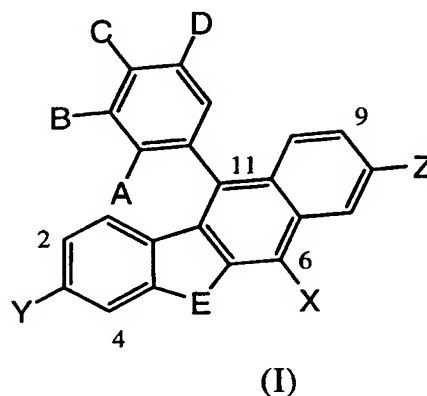
Example 217.**[2,6-Dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-3-hydroxy-phenoxy]-acetic acid**

To a solution of [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-3-hydroxy-phenol (1.28g, 2.27mmole) in anhydrous tetrahydrofuran (64mL) was added triphenylphosphine (1.193g, 4.55mmole), methyl glycolate (0.351mL, 4.55mmol) and diethylazodicarboxylate (0.305mL, 4.55 mmole) at room temperature under a dry nitrogen atmosphere. After stirring at room temperature for 8 days the reaction was quenched with water (10mL) and the solvents were removed. The yellow residual solid was taken up in a mixture of methylene chloride, ether, and ethyl acetate and combined with silica gel. The solvents were removed and the adsorbate was flash chromatographed (40 / 60 petroleum ether / methylene chloride) to provide a white solid (0.342g, 24%). To a solution of this solid (0.490 g, 0.772 mmol) in tetrahydrofuran (6 mL) and methanol (2 mL) was added a 0.5 M aqueous solution of potassium hydroxide (3.24 mL, 1.62 mmol, 2.1 eq) dropwise at room temperature. After stirring 1.5 hours at room temperature the solvents were removed and the residue was combined with water. After removing impurities with diethyl ether (20 mL), the aqueous phase was acidified with 10% aqueous hydrochloric acid. The organics were extracted with diethyl ether. The extracts were combined, concentrated, and chased several times with benzene and dried in vacuo at 60°C to provide the title compound as an off-white solid (0.380 g, 79%): mp 194-240°C; NMR (DMSO, d₆): δ 13.15 (s, 1H), 9.58 (s, 1H, OH), 8.35 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.78 (ddd, J = 8, 7, 1 Hz, 1H), 7.67 - 7.57 (m, 4H), 7.31 (t, J = 8 Hz, 1H), 6.94 - 6.92 (m, 1H), 4.70 (s, 2H); MS (+FAB): [M+], 3 bromine isotope pattern, 618 (34%), 620 (100%), 622 (100%), 624 (34%); Anal. Calc. for C₂₄H₁₃Br₃O₅: C, 46.41, H, 2.11, N, 0.00. Found: C, 46.78, H, 2.05,

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WHAT IS CLAIMED IS:

1. A compound of formula I having the structure



5

wherein

A is hydrogen, halogen, or OH;

B and D are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, nitro, amino or OR;

- 10 R is hydrogen, alkyl of 1-6 carbon atoms, $-\text{COR}^1$, $-\text{CH}_2\text{CO}_2\text{R}^1$, $-\text{CH}(\text{R}^{1a})\text{CO}_2\text{R}^1$, or $-\text{SO}_2\text{R}^1$;

R^1 and R^{1a} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms or aryl;

E is S, SO, SO_2 , O;

- 15 X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon atoms, nitro, amino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl, or $-\text{OCH}_2\text{CO}_2\text{R}^{1b}$;

R^{1b} is hydrogen or alkyl of 1-6 carbon atoms;

- 20 Y and Z are each, independently, hydrogen or OR^2 ;

R^2 is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or $-\text{CH}_2\text{CO}_2\text{R}^3$;

R^3 is hydrogen or alkyl of 1-6 carbon atoms;

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- C is hydrogen, halogen or OR⁴;
- R⁴ is hydrogen, alkyl of 1-6 carbon atoms, -CH(R⁵)W, -C(CH₃)₂CO₂R⁶,
5-thiazolidine-2,4-dione, -CH(R⁷)CH₂CO₂R⁶, -COR⁶, PO₃(R⁶)₂, or -SO₂R⁶;
- R⁵ is hydrogen, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH₂(1H-imidazol-4-yl),
5 -CH₂(3-1H-indolyl), -CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl),
-CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), -CH₂(3-pyridyl), or
-CH₂CO₂H;
- W is -CO₂R⁶, -CONH₂, -CONHOH, CN, -CONH(CH₂)₂CN, 5-tetrazole, -PO₃(R⁶)₂,
-CH₂OH, or -CH₂Br, -CONR⁶CHR⁷CO₂R⁸,
- 10 R⁶ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;
R⁷ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;
R⁸ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;
or a pharmaceutically acceptable salt thereof.
- 15 2. The compound according to claim 1, wherein
A and B are each, independently, hydrogen, or bromine;
C and D are OH;
E is S, or O;
X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, alkoxy of 1-6 carbon atoms,
20 aryloxy of 6-12 carbon atoms; arylalkoxy of 6-12 carbon atoms, arylsulfanyl,
or pyridylsulfanyl;
Y and Z are H;
or a pharmaceutically acceptable salt thereof.
- 25 3. The compound according to claim 1, wherein
A is hydrogen;
B and D are each, independently, halogen, alkyl of 1-6 carbon atoms, aryl or aralkyl
of 6-12 carbon atoms, or alkoxy of 1-6 carbon atoms;
C is OR⁴;

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E is S, O;

X is hydrogen, halogen, alkyl of 1-6 carbon atoms, perfluoroalkyl of 1-6 carbon atoms, CN, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon atoms, arylsulfanyl, pyridylsulfanyl;

5 Y and Z are H;

R⁴ is H, alkyl of 1-6 carbon atoms, -CH(R⁵)W, or 5-thiazolidine-2,4-dione;

R⁵ is H, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, aryl, -CH₂(3-1H-indolyl), -CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl), -CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), or -CH₂(3-pyridyl);

10 W is -CO₂R⁶, -CONH₂, -CONHOH, -5-tetrazole, or -PO₃(R⁶)₂;

R⁶ is hydrogen or alkyl of 1-6 carbon atoms;
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-bromo-
15 benzo[b]naphtho[2,3-d]furan-11-yl)-phenoxy]-3-phenyl-propionic acid or a
pharmaceutically acceptable salt thereof.

5. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-bromo-
benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid or a
20 pharmaceutically acceptable salt thereof.

6. The compound of claim 1, which is (5'-benzo[b]naphtho[2,3-d]-
thiophen-11-yl)-[1,1';3',1'']terphenyl-2'-yloxy)-acetic acid or a pharmaceutically
acceptable salt thereof.

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7. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-iodo-
benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid or a
pharmaceutically acceptable salt thereof.

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8. The compound of claim 1, which is 2-[2,6-dibromo-4-(6-bromo-benzo-
[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(4-fluoro-phenyl)-propionic acid or a
pharmaceutically acceptable salt thereof.
- 5 9. The compound of claim 1, which is (R)-2-[2-bromo-4-(6-bromo-
benzo[b]naphtho[2,3-d]thiophen-11-yl)-6-methoxy-phenoxy]-3-phenyl-propionic acid
or a pharmaceutically acceptable salt thereof.
- 10 10. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-bromo-
benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid or a
pharmaceutically acceptable salt thereof.
- 15 11. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-iodo-
benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid or a
pharmaceutically acceptable salt thereof.
- 20 12. The compound of claim 1, which is 2-[2,6-dibromo-4-(6-bromo-benzo-
[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-hexanoic acid or a pharmaceutically
acceptable salt thereof.
- 25 13. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-methoxy-
benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid or a
pharmaceutically acceptable salt thereof.
14. The compound of claim 1, which is (R)-2-{2,6-dibromo-4-(6-chloro-
benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy}-3-phenyl-propionic acid or a
pharmaceutically acceptable salt thereof.

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15. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-phenyl-sulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid or a pharmaceutically acceptable salt thereof.
- 5 16. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-phenyl-sulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid or a pharmaceutically acceptable salt thereof.
- 10 17. The compound of claim 1, which is (R,S)-2-[2,6-dibromo-4-(6-bromobenzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(1H-indol-3-yl)-propionic acid or a pharmaceutically acceptable salt thereof.
- 15 18. The compound of claim 1, which is (R)-benzo[b]naphtho[2,3-d]thiophen-11-yl-2,6-diiodo-phenoxy)-3-phenyl-propionic acid or a pharmaceutically acceptable salt thereof.
- 20 19. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-bromobenzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-butyric acid or a pharmaceutically acceptable salt thereof.
- 25 20. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid or a pharmaceutically acceptable salt thereof.
- 20 21. The compound of claim 1, which is (S)-2-[2,6-dibromo-4-(6-bromobenzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-butyric acid or a pharmaceutically acceptable salt thereof.

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22. The compound of claim 1, which is (R)-2-(4-benzo[b]naphtho[2,3-d]-thiophen-11-yl-2,6-dibromo-phenoxy)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid or a pharmaceutically acceptable salt thereof.

5 23. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid or a pharmaceutically acceptable salt thereof.

10 24. The compound of claim 1, which is {1-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propyl}-phosphonic acid, diethyl ester or a pharmaceutically acceptable salt thereof.

15 25. The compound of claim 1, which is (R)-2-{2,6-dibromo-4-[6-(pyridin-4-ylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenoxy}-3-phenyl-propionic acid or a pharmaceutically acceptable salt thereof.

20 26. The compound of claim 1, which is (R)-2-[4-(6-benzyloxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dibromo-phenoxy]-3-phenyl-propionic acid or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1, which is (S)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester or a pharmaceutically acceptable salt thereof.

25 28. The compound of claim 1, which is (R)-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-phenyl-acetic acid or a pharmaceutically acceptable salt thereof.

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29. The compound of claim 1, which is [2,6-dibromo-4-(6-bromo-benzo-
[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid or a pharmaceutically
acceptable salt thereof.

5 30. The compound of claim 1, which is [2,6-dibromo-4-(6-bromo-benzo-
[b]naphtho[2,3-d]thiophen-11-yl)-phoxymethyl]-phosphonic acid or a
pharmaceutically acceptable salt thereof.

10 31. The compound of claim 1, which is [2,6-dibromo-4-(6-cyano-benzo-
[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid or a pharmaceutically
acceptable salt thereof.

15 32. The compound of claim 1, which is 2-[2,6-dibromo-4-(6-bromo-benzo-
[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-naphthalen-2-yl-propionic acid or a
pharmaceutically acceptable salt thereof.

20 33. The compound of claim 1, which is (2R)-2-[2,6-dibromo-4-(6-bromo-
benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1-oxo-1,3-dihydro-isoindol-2-
yl)-butyric acid or a pharmaceutically acceptable salt thereof.

 34. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-methyl-
benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid or a
pharmaceutically acceptable salt thereof.

25 35. The compound of claim 1, which is (R)-5-{1-[2,6-dibromo-4-(6-
bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-2-phenyl-ethyl}-1H-
tetrazole or a pharmaceutically acceptable salt thereof.

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36. The compound of claim 1, which is (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-N-hydroxy-3-phenyl-propionamide or a pharmaceutically acceptable salt thereof.

5 37. The compound of claim 1, which is 5-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-thiazolidinedione-2,4-dione or a pharmaceutically acceptable salt thereof.

38. The compound of claim 1, which is (R)-2-(4-benzo[b]naphtho[2,3-d]-thiophen-11-yl-2,6-diiodo-phenoxy)-propionic acid or a pharmaceutically acceptable salt thereof.

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39. The compound of claim 1, which is 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-pyridin-3-yl-propionic acid

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40. The compound of claim 1, which is (2R)-2-[4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenoxy]-3-phenyl-propionic acid or a pharmaceutically acceptable salt thereof.

20 41. The compound of claim 1, which is 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenol or a pharmaceutically acceptable salt thereof.

42. The compound of claim 1, which is 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol or a pharmaceutically acceptable salt thereof.

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43. The compound of claim 1, which is 3-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol or a pharmaceutically acceptable salt thereof.

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44. The compound of claim 1, which is 4-bromo-5-(6-bromo-benzo[b]-naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol or a pharmaceutically acceptable salt thereof.

5 45. The compound of claim 1, which is [2, 6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-phenoxy]-acetic acid or a pharmaceutically acceptable salt thereof.

46. The compound of claim 1, which is 2, 6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-phenol or a pharmaceutically acceptable salt thereof.

47. The compound of claim 1, which is [4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenoxy]-acetic acid or a pharmaceutically acceptable salt thereof.

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48. The compound of claim 1, which is
4-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol;
11-(4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-ol;
4-(6-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenol;
20 3-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-benzene-1,2-diol;
8-methoxy-11-(4-methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene;
11-(4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-8-ol;
2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
25 11-(3,5-dibromo-4-methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene;
11-(4-methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene;
11-(4-methoxy-3,5-dimethyl-phenyl)-6-methyl-benzo[b]naphtho[2,3-d]thiophene;
2,6-dimethyl-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diiodo-phenol;
30 4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-iodo-phenol;

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- 11-(4-methoxy-3,5-diiodo-phenyl)-benzo[b]naphtho[2,3-d]thiophene;
11-(3-iodo-4-methoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene;
5-benzo[b]naphtho[2,3-d]thiophen-11-yl-2-methoxy-isophthalonitrile;
5-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-methoxy-benzonitrile;
5 5-benzo[b]naphtho[2,3-d]thiophen-11-yl-2-hydroxy-isophthalonitrile;
5-benzo[b]naphtho[2,3-d]thiophen-11-yl-2-hydroxy-benzonitrile;
4-(benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol) acetate ester;
acetic acid 3-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenyl ester;
acetic acid 2-acetoxy-4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester;
10 4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenol) acetate;
acetic acid 3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester;
acetic acid 2-acetoxy-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester;
4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
15 11-(4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene-6-carbonitrile;
methanesulfonic acid 4-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenyl ester;
methanesulfonic acid 4-(6-chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester;
methanesulfonic acid 4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester;
methanesulfonic acid 4-(6-trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-
20 phenyl ester;
methanesulfonic acid 4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester;
4-(6-chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
4-(6-trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
25 4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
4-(6-methoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
4-(6-phenylsufanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
4-[6-(2-dimethylamino-ethylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol;
4-[6-(pyridin-4-ylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol;
30 11-(3,5-dibromo-4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophene-6-carbonitrile;

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- 2,6-dibromo-4-(6-iodo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
2,6-dibromo-4-(6-chloro-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
2,6-dibromo-4-(6-trifluoromethyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
2,6-dibromo-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
5 2,6-dibromo-4-(6-methoxybenzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
2,6-dibromo-4-(6-phenylsulfanyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
2,6-dibromo-4-[6-(pyridin-4-ylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol;
2,6-dibromo-4-[6-(2-dimethylamino-ethylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenol;
10 11-yl)-phenol;
2,6-dichloro-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
2-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
2,4-dibromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenol;
[11-(4-hydroxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-yloxy]-acetic acid methyl
15 ester;
[11-(4-methoxycarbonylmethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-yloxy]-acetic acid methyl ester;
[11-(4-carboxymethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-3-yloxy]-acetic acid;
[11-(4-methoxycarbonylmethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-8-yloxy]-
20 acetic acid, methyl ester;
[11-(4-carboxymethoxy-phenyl)-benzo[b]naphtho[2,3-d]thiophen-8-yloxy]-acetic acid;
[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid, methyl ester;
[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic
25 acid, tert-butyl ester;
[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid, sodium salt;
[(4-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dicyano-phenoxy]-acetic acid;
[(4-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-cyano-phenoxy]-acetic acid;
30 (4-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diiodo-phenoxy)-acetic acid;

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- [4-benzo[b]naphtho[2,3-d]thiophen-11-yl-phenoxy]-acetic acid;
(4-benzo[b]naphtho[2,3-d]thiophen-11-yl-2-iodo-phenoxy)-acetic acid;
{2,6-dimethyl-4-[6-methyl-(benzo[b]naphtho[2,3-d]thiophen-11-yl)]-phenoxy}-acetic acid;
- 5 [4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid;
[3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid;
[2-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid;
[2,4-dibromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetic acid;
- 10 5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-carboxymethoxy-phenoxy]-acetic acid;
3-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-carboxymethoxy-phenoxy]-acetic acid;
4-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-carboxymethoxy-
- 15 phenoxy]-acetic acid;
(R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester;
(R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, sodium salt;
- 20 (S)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
(R)-2-[2,6-dibromo-4-(6-methoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester;
(S)-2-[4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-
- 25 propionic acid;
(S)-2-[2,6-dibromo-4-(6-cyano-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
(R)-2-[4-(6-cyano-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- 30 (R)-2-[4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;

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- (R)-2-[4-(3-carboxymethoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy-3-phenyl-propionic acid;
- (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(1H-imidazol-4-yl)-propionic acid, hydrochloride;
- 5 (R)-2-[2,6-dichloro-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- (R)-2-{2,6-dibromo-4-[6-(2-dimethylamino-ethylsulfanyl)-benzo[b]naphtho[2,3-d]thiophen-11-yl]-phenoxy}-3-phenyl-propionic acid;
- (R)-2-[2,6-dimethyl-4-(6-methyl-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- 10 (R)-2-[4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-diisopropyl-phenoxy]-propionic acid;
- (S)-2-[2-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid;
- 15 (R)-2-[2-bromo-5-(6-Bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid;
- (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid, methyl ester;
- (R)-2-[4-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid;
- 20 (R)-2-[4-(3-carboxymethoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid;
- (R)-2-[4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid;
- 25 (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-succinic acid dimethyl ester;
- (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-succinic acid;
- 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-(4-fluoro-phenyl-propionic acid tert-butyl ester;
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- (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-naphthalen-2-yl-propionic acid tert-butyl ester;
 {2,6-dibromo-4-[6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl]}-phoxymethyl}-phosphonic acid diethyl ester;
- 5 [4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phoxymethyl]-phosphonic acid diethyl ester;
 [4-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-phoxymethyl]-phosphonic acid;
 {1-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propyl}-phosphonic acid;
- 10 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetamide;
 (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionamide;
 (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-N-
- 15 (3-nitrolo-propyl)3-phenyl-propionamide;
 [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-acetonitrile;
 (R)-2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionitrile;
- 20 5-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phoxymethyl]-1H-tetrazole;
 (R)-6-bromo-11-[3,5-dibromo-4-(1-hydroxymethyl-2-phenyl-ethoxy)-phenyl]-benzo[b]naphtho[2,3-d]thiophene;
 (R)-6-bromo-11-[3,5-dibromo-4-(1-bromomethyl-2-phenyl-ethoxy)-phenyl]-
- 25 benzo[b]naphtho[2,3-d]thiophene;
 phosphoric acid di-tert-butyl ester 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl ester;
 phosphoric acid mono-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenyl] ester;

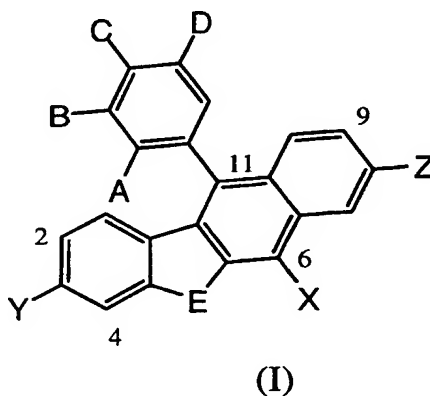
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- 2-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-2-methyl-propionic acid;
- 3-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-propionic acid;
- 5 (R)-3-[2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-butyric acid;
- (R)-2-[4-(6-hydroxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dibromo-phenoxy]-3-phenyl-propionic acid, methyl ester;
- (R)-2-[4-(6-benzyloxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-dibromo-10 phenoxy]-3-phenyl-propionic acid, methyl ester;
- (R)-2-[2,6-dibromo-4-(6-methoxycarbonylmethoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid methyl ester;
- (R)-2-[2,6-dibromo-4-(6-carboxymethoxy-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- 15 [2,6-dibromo-4-(6-bromo-5,5-dioxo-5H-6-benzo[b]naphtho[2,3-d]thiophen-11-yl)]-phenoxy]-acetic acid;
- [2,6-dibromo-4-[6-bromo-5-oxo-5H-4-benzo[b]naphtho[2,3-d]thiophen-11-yl)]-phenoxy]-acetic acid;
- (R)-2-[2,6-dibromo-4-(6-bromo-5,5-dioxo-5H-5(λ 6)-benzo[b]naphtho[2,3-d]-20 thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid, methyl ester;
- (R)-2-[2,6-dibromo-4-(6-bromo-5,5-dioxo-5H-5(λ 6)-benzo[b]naphtho[2,3-d]thiophen-11-yl)-phenoxy]-3-phenyl-propionic acid;
- 5'-benzo[b]naphtho[2,3-d]thiophen-11-yl-[1,1';3',1'']terphenyl-2'-ol
- 3-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-benzyloxy-phenol;
- 25 2-bromo-4-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-6-methoxy-phenol;
- 3-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-methoxy-phenol;
- (R)-2-[3-bromo-5-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2-methoxy-phenoxy]-3-phenyl-propionic acid;
- 3-(benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6 difluoro-phenol;
- 30 3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6 difluoro-phenol;

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- [3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenoxy]-acetic acid;
- (R)-2-[3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenoxy]-propionic acid;
- 5 (R)-2-[3-(6-bromo-benzo[b]naphtho[2,3-d]thiophen-11-yl)-2,6-difluoro-phenoxy]-3-phenyl-propionic acid;
- 4-benzo[b]naphtho[2,3-d]furan-11-yl)-phenol;
- 4-(benzo[b]naphtho[2,3-d]furan-11-yl)-benzene-1,3-diol;
- 2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-3-hydroxy-phenol;
- 10 4-(benzo[b]naphtho[2,3-d]furan-11-yl-phenoxy)-acetic acid methy ester;
- 4-(benzo[b]naphtho[2,3-d]furan-11-yl-phenoxy)-acetic acid;
- [2, 6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan -11-yl)-phenoxy]-acetic acid methyl ester; or
- [2,6-dibromo-4-(6-bromo-benzo[b]naphtho[2,3-d]furan-11-yl)-3-hydroxy-phenoxy]-
- 15 acetic acid;
- or a pharmaceutically acceptable salt thereof.

49. A method of treating metabolic disorders mediated by insulin resistance or hyperglycemia in a mammal in need thereof which comprises
- 20 administering to said mammal, a compound of formula I having the structure



wherein

A is hydrogen, halogen, or OH;

- 198 -

B and D are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, nitro, amino or OR;

R is hydrogen, alkyl of 1-6 carbon atoms, $-\text{COR}^1$, $-\text{CH}_2\text{CO}_2\text{R}^1$, $-\text{CH}(\text{R}^{1a})\text{CO}_2\text{R}^1$, or $-\text{SO}_2\text{R}^1$;

5 R^1 and R^{1a} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms or aryl;

E is S, SO, SO_2 , O;

X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon atoms, nitro, amino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl, or $-\text{OCH}_2\text{CO}_2\text{R}^{1b}$;

R^{1b} is hydrogen or alkyl of 1-6 carbon atoms;

Y and Z are each, independently, hydrogen or OR^2 ;

R^2 is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or $-\text{CH}_2\text{CO}_2\text{R}^3$;

R^3 is hydrogen or alkyl of 1-6 carbon atoms;

C is hydrogen, halogen or OR^4 ;

R^4 is hydrogen, alkyl of 1-6 carbon atoms, $-\text{CH}(\text{R}^5)\text{W}$, $-\text{C}(\text{CH}_3)_2\text{CO}_2\text{R}^6$, 5-thiazolidine-2,4-dione, $-\text{CH}(\text{R}^7)\text{CH}_2\text{CO}_2\text{R}^6$, $-\text{COR}^6$, $\text{PO}_3(\text{R}^6)_2$, or $-\text{SO}_2\text{R}^6$;

20 R^5 is hydrogen, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $-\text{CH}_2(3-1\text{H-indolyl})$, $-\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$, $-\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $-\text{CH}_2(3\text{-pyridyl})$, or $-\text{CH}_2\text{CO}_2\text{H}$;

W is $-\text{CO}_2\text{R}^6$, $-\text{CONH}_2$, $-\text{CONHOH}$, CN, $-\text{CONH}(\text{CH}_2)_2\text{CN}$, 5-tetrazole, $-\text{PO}_3(\text{R}^6)_2$, $-\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{Br}$, $-\text{CONR}^6\text{CHR}^7\text{CO}_2\text{R}^8$;

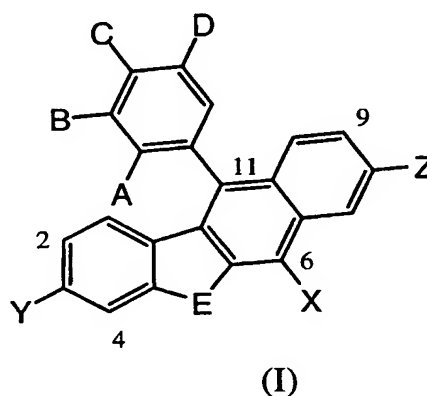
R^6 is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

R^7 is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

- 199 -

R^8 is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;
or a pharmaceutically acceptable salt thereof.

50. A method of treating or inhibiting type II diabetes in a mammal in
need thereof which comprises administering to said mammal, a compound of formula
I having the structure



wherein

A is hydrogen, halogen, or OH;

- 10 B and D are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms,
aryl, aralkyl of 6-12 carbon atoms, nitro, amino or OR;

R is hydrogen, alkyl of 1-6 carbon atoms, $-\text{COR}^1$, $-\text{CH}_2\text{CO}_2\text{R}^1$, $-\text{CH}(\text{R}^{1a})\text{CO}_2\text{R}^1$, or
 $-\text{SO}_2\text{R}^1$;

- R^1 and R^{1a} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aralkyl of
15 6-12 carbon atoms or aryl;

E is S, SO, SO_2 , O;

- X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon
atoms, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon
atoms, nitro, amino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl,
20 pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl, or $-\text{OCH}_2\text{CO}_2\text{R}^{1b}$;

R^{1b} is hydrogen or alkyl of 1-6 carbon atoms;

Y and Z are each, independently, hydrogen or OR^2 ;

- 200 -

R^2 is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or
 $-\text{CH}_2\text{CO}_2R^3$;

R^3 is hydrogen or alkyl of 1-6 carbon atoms;

C is hydrogen, halogen or OR^4 ;

5 R^4 is hydrogen, alkyl of 1-6 carbon atoms, $-\text{CH}(R^5)W$, $-\text{C}(\text{CH}_3)_2\text{CO}_2R^6$,
 5-thiazolidine-2,4-dione, $-\text{CH}(R^7)\text{CH}_2\text{CO}_2R^6$, $-\text{COR}^6$, $\text{PO}_3(R^6)_2$, or $-\text{SO}_2R^6$;

R^5 is hydrogen, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$,
 $-\text{CH}_2(3\text{-1H-indolyl})$, $-\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$,
 $-\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $-\text{CH}_2(3\text{-pyridyl})$, or

10 $-\text{CH}_2\text{CO}_2\text{H}$;

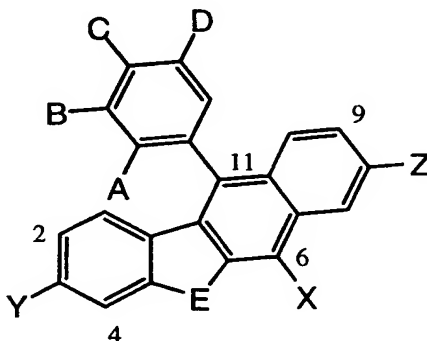
W is $-\text{CO}_2R^6$, $-\text{CONH}_2$, $-\text{CONHOH}$, CN, $-\text{CONH}(\text{CH}_2)_2\text{CN}$, 5-tetrazole, $-\text{PO}_3(R^6)_2$,
 $-\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{Br}$, $-\text{CONR}^6\text{CHR}^7\text{CO}_2R^8$,

R^6 is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

R^7 is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

15 R^8 is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;
 or a pharmaceutically acceptable salt thereof.

51. A method of modulating glucose levels in a mammal in need thereof
 which comprises administering to said mammal, a compound of formula I having the
 structure



(I)

20

wherein

A is hydrogen, halogen, or OH;

- 201 -

B and D are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, nitro, amino or OR;

R is hydrogen, alkyl of 1-6 carbon atoms, $-\text{COR}^1$, $-\text{CH}_2\text{CO}_2\text{R}^1$, $-\text{CH}(\text{R}^{1a})\text{CO}_2\text{R}^1$, or $-\text{SO}_2\text{R}^1$;

5 R^1 and R^{1a} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms or aryl;

E is S, SO, SO_2 , O;

X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon atoms, nitro, amino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl, or $-\text{OCH}_2\text{CO}_2\text{R}^{1b}$;

10

R^{1b} is hydrogen or alkyl of 1-6 carbon atoms;

Y and Z are each, independently, hydrogen or OR^2 ;

R^2 is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or $-\text{CH}_2\text{CO}_2\text{R}^3$;

15

R^3 is hydrogen or alkyl of 1-6 carbon atoms;

C is hydrogen, halogen or OR^4 ;

R^4 is hydrogen, alkyl of 1-6 carbon atoms, $-\text{CH}(\text{R}^5)\text{W}$, $-\text{C}(\text{CH}_3)_2\text{CO}_2\text{R}^6$, 5-thiazolidine-2,4-dione, $-\text{CH}(\text{R}^7)\text{CH}_2\text{CO}_2\text{R}^6$, $-\text{COR}^6$, $\text{PO}_3(\text{R}^6)_2$, or $-\text{SO}_2\text{R}^6$;

20 R^5 is hydrogen, alkyl of 1-6 carbon atoms, aralkyl, aryl, $\text{CH}_2(1\text{H-imidazol-4-yl})$, $-\text{CH}_2(3\text{-1H-indolyl})$, $-\text{CH}_2\text{CH}_2(1,3\text{-dioxo-1,3-dihydro-isoindol-2-yl})$, $-\text{CH}_2\text{CH}_2(1\text{-oxo-1,3-dihydro-isoindol-2-yl})$, $-\text{CH}_2(3\text{-pyridyl})$, or $-\text{CH}_2\text{CO}_2\text{H}$;

W is $-\text{CO}_2\text{R}^6$, $-\text{CONH}_2$, $-\text{CONHOH}$, CN, $-\text{CONH}(\text{CH}_2)_2\text{CN}$, 5-tetrazole, $-\text{PO}_3(\text{R}^6)_2$, $-\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{Br}$, $-\text{CONR}^6\text{CHR}^7\text{CO}_2\text{R}^8$;

25

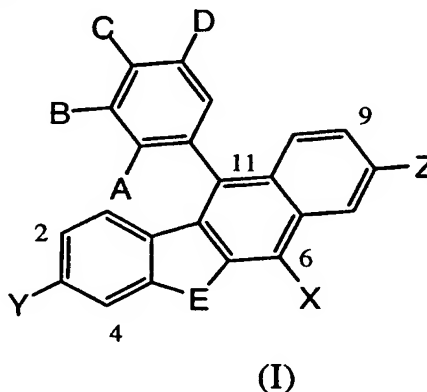
R^6 is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

R^7 is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

- 202 -

R^8 is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;
or a pharmaceutically acceptable salt thereof.

52. A pharmaceutical composition which comprises a compound of
5 formula I having the structure



wherein

- A is hydrogen, halogen, or OH;
B and D are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms,
10 aryl, aralkyl of 6-12 carbon atoms, nitro, amino or OR;
R is hydrogen, alkyl of 1-6 carbon atoms, $-\text{COR}^1$, $-\text{CH}_2\text{CO}_2\text{R}^1$, $-\text{CH}(\text{R}^{1a})\text{CO}_2\text{R}^1$, or
 $-\text{SO}_2\text{R}^1$;
 R^1 and R^{1a} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aralkyl of
6-12 carbon atoms or aryl;
15 E is S, SO, SO_2 , O;
X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon
atoms, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon
atoms, nitro, amino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl,
pyridylsulfanyl, 2-N,N-dimethylaminoethylsulfanyl, or $-\text{OCH}_2\text{CO}_2\text{R}^{1b}$;
20 R^{1b} is hydrogen or alkyl of 1-6 carbon atoms;
Y and Z are each, independently, hydrogen or OR^2 ;
 R^2 is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or
 $-\text{CH}_2\text{CO}_2\text{R}^3$;

- 203 -

R³ is hydrogen or alkyl of 1-6 carbon atoms;

C is hydrogen, halogen or OR⁴;

R⁴ is hydrogen, alkyl of 1-6 carbon atoms, -CH(R⁵)W, -C(CH₃)₂CO₂R⁶,
5-thiazolidine-2,4-dione, -CH(R⁷)CH₂CO₂R⁶, -COR⁶, PO₃(R⁶)₂, or -SO₂R⁶;

5 R⁵ is hydrogen, alkyl of 1-6 carbon atoms, aralkyl, aryl, CH₂(1H-imidazol-4-yl),
-CH₂(3-1H-indolyl), -CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl),
-CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), -CH₂(3-pyridyl), or
-CH₂CO₂H;

W is -CO₂R⁶, -CONH₂, -CONHOH, CN, -CONH(CH₂)₂CN, 5-tetrazole, -PO₃(R⁶)₂,
10 -CH₂OH, or -CH₂Br, -CONR⁶CHR⁷CO₂R⁸,

R⁶ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

R⁷ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

R⁸ is hydrogen, alkyl of 1-6 carbon atoms, aryl or aralkyl;

or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier.

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 99/10185

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D333/74 C07D307/77 A61K31/38 A61K31/34 C07D409/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 97, no. 7, 16 August 1982 (1982-08-16) Columbus, Ohio, US; abstract no. 55625, KANO, SHINZO ET AL: "A synthesis of benzo'b!naphtho'2,3-d!thiophene derivatives via benzo'b!thiophene-2,3-quinodimethane intermediates" XP002114980 cited in the application abstract & HETEROCYCLES (1982), 19(6), 1033-7 , --- -/--	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 September 1999

Date of mailing of the international search report

28/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Bosma, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10185

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HASTINGS, J. S. ET AL: "Overcrowded molecules. VIII. Addition of diphenylketene to (Z)-2-benzylidene-3-(diphenylmethylene)-2,3-dihydro-5-methylbenzofuran" J. CHEM. SOC., PERKIN TRANS. 1 (1972), (14), 1839-42, XP002114978 cited in the application compounds 11	1
A	----- HASTINGS, JOHN S. ET AL: "Overcrowded molecules. XII. Thermal and photochemical reactions of (2Z,3Z)- and (2Z,3E)-2-benzylidene-2,3-dihydro-3-mesityl(phenyl)methylenebenzofuran" J. CHEM. SOC., PERKIN TRANS. 1 (1975), (19), 1995-8, XP002114979 cited in the application compound 9a	1
A	----- EP 0 816 352 A (CIRD GALDERMA) 7 January 1998 (1998-01-07) claims 1,3-7 -----	1,49

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/10185

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 40-52
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 40-52
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/10185

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0816352 A	07-01-1998	FR 2750426 A	02-01-1998
		AU 701277 B	21-01-1999
		AU 2559497 A	15-01-1998
		CA 2209391 A	28-12-1997
		JP 10067765 A	10-03-1998
		US 5905088 A	18-05-1999
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WORLD INTELLECT
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INTERNATIONAL APPLICATION PUBLISHED



WO 9603377A1

(51) International Patent Classification 6 :

C07D 209/88, 209/86, 209/42, 209/08,
495/04, 471/04, 403/06, 403/04, 401/06,
A61K 31/41, 31/40

A

(43) International Publication Date: 8 February 1996 (08.02.96)

(21) International Application Number: PCT/JP95/01494

(22) International Filing Date: 27 July 1995 (27.07.95)

(30) Priority Data:

9415175.0 27 July 1994 (27.07.94) GB
9423948.0 25 November 1994 (25.11.94) GB(71) Applicant (for all designated States except US): SANKYO
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100 (JP).(81) Designated States: AU, CA, CN, CZ, FI, HU, JP, KR, MX,
NO, NZ, RU, US, European patent (AT, BE, CH, DE, DK,
ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

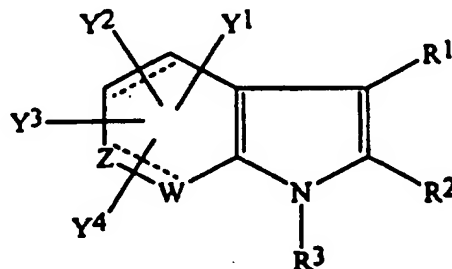
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With international search report.

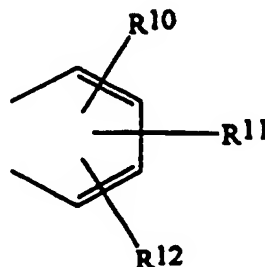
(54) Title: HETEROCYCLIC COMPOUNDS, USEFUL AS ALLOSTERIC EFFECTORS AT MUSCARINIC RECEPTORS

(57) Abstract

Compounds of formula (I) wherein Z represents a methylene group, a methine group, a group of formula $>NH$ or a group of formula $>N-$, and W represents a methylene group, a methine group, a sulfur atom or a group of formula $\mu S \rightarrow (O)_v$, where μ is 1 or 2; \rightarrow is a single or double bond; at least one of Y^1 , Y^2 , Y^3 and Y^4 represents a carboxyl group, a sulfonamide group or a group of formula $-(A)_p-B^1-T^1$, wherein A is S or O, T^1 is a carboxyl group, a thiocarboxy group, a dithiocarboxy group, a sulfonamide group or a tetrazolyl group, B^1 is a bond, an optionally substituted alkylene group and p is 0 or 1; the rest of Y^1 , Y^2 , Y^3 and Y^4 are the same or different and are H, halogen, nitro, OH, SH, NH_2 , optionally substituted alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, aryl, aralkyloxy, aralkylthio and $Y^1 + Y^2$ may together be a lactone or keto; one of R^1 and R^2 is H, alkyl, alkanoyl, aryl, arylcarbonyl, aralkyl, carboxyl, sulfonamide or a group of formula $-(O)_q-B^2-T^2$, wherein T^2 is COOH, sulfonamide or tetrazolyl, B^2 is an optionally substituted alkylene, and q is 0 or 1; the other of R^1 and R^2 is H, alkyl, aryl or aralkyl, or R^1 and R^2 together represent a group of formula (Ib'), wherein R^{10} , R^{11} and R^{12} are the same or different and each is H, OH, halogen, haloalkyl, optionally substituted alkyl, alkoxy, alkylthio, alkylsulfinyl or alkylsulfonyl; R^3 is H or an amino protecting group; and pharmaceutically acceptable salts and esters thereof are allosteric effectors at muscarinic receptors, and are useful in the treatment and prophylaxis of disorders associated with muscarinic receptors.



(I)



(Ib')

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
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CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

HETEROCYCLIC COMPOUNDS, USEFUL AS ALLOSTERIC EFFECTORS AT MUSCARINIC RECEPTORS

Field of the Invention

The present invention relates to compounds useful as allosteric effectors at muscarinic receptors, to uses of such compounds and to the synthesis of such compounds.

Prior Art

Acetylcholine is known to be associated with memory, and it is also known that there are decreased levels of acetylcholine in the brain in sufferers of Alzheimer's Disease.

In an attempt to provide a cure for Alzheimer's Disease, various groups have endeavoured to alleviate the cholinergic deficit in vivo. This has been done, for example, by using cholinesterase inhibitors (to reduce the rate of acetylcholine breakdown) or by using alternative agonists to serve as a supplement to acetylcholine.

Neither course of action has proved successful, as the effect of each is generalised, so that acetylcholine throughout the body and at all receptors is prevented from breaking down, or supplemented (or both), without specifically targetting those receptors involved in Alzheimer's disease. Enhancing the effect of acetylcholine at some receptors can cause depression, for example, so that these courses of action are not being pursued.

More specifically, acetylcholine acts at receptors

which fall into two classes; muscarinic and nicotinic. It is believed that the muscarinic receptors are involved in Alzheimer's disease.

The muscarinic receptors belong to the family of G-protein coupling receptors, and have been classified into three subtypes on the basis of their pharmacological properties and into five subtypes from their molecular structures. The nomenclature of muscarinic receptor subtypes has been confused, and, at the Fourth International Symposium on Muscarinic Receptors, it was recommended that subtypes based on the antagonist binding properties be referred to as M_1 , M_2 , M_3 , M_4 and that those based on molecular structure be called m1-m5 (see below). This nomenclature is used hereinafter.

Muscarinic receptor nomenclature

Pharmacological characterization

Subtype	M_1	M_2	M_3	M_4
Selective antagonists	pzpine (+)-tzipne	AF-DX 116, himbacine, m/tramine, gallamine*	p-fluoro- hexahydrosila- difenidol, hexahydrosila- difenidol	tropicamide

Molecular characterization

Sequences	m1	m2	m3	m4	m5
Numbers of amino acids	460	466	589/590	478/479	531/532

pzpine = pirenzepine; tzipne = telenzepine;
m/tramine = methoctramine; * not competitive;

Recently, it has been possible to use cells expressing m1-m5 receptors. These cells are pure

preparations of each receptor subtype and are very useful for characterizing each subtype and for screening for subtype specific agents.

Studies have been performed on muscarinic receptors in the heart (M2) using the antagonist N-methyl-scopolamine (NMS), and these have established that the binding of this antagonist can be affected by other agents, but that these agents do not necessarily act at the NMS binding site. Such action at a different binding site is known as allosteric action, or allosterism. Tucek et al. [J. Neurochem. (1993), 61, Suppl., S19] have shown that the neuromuscular blocking drug, alcuronium, allosterically increases the affinity of M2 muscarinic receptors in the heart for NMS.

It was reported by Riker and Wescoe in 1951 that gallamine had a negative action on heart receptors [Ann. N. Y. Acad. Sci., 54, 373-94 (1951)]. It was subsequently established that gallamine was not a competitive antagonist for acetylcholine.

Waelbroeck et al. [J. Recep. Res., 8, 787-808 (1988)] reported that curare acts allosterically against muscarinic receptors in the brain, but these results cannot be repeated.

Tubocurarine and batrachotoxin have also been reported to have negative allosteric effects on antagonist binding.

Birdsall et al. [Pierre Fabre Monograph Series, 1, New Concepts in Alzheimer's Disease, Ed's Briley, M., et al., Macmillan Press, Chapter 9, 103-121] speculate that "the muscarinic receptor sub-types exhibit a selectivity in their binding profile for allosteric agents, and it may hence be possible to selectively 'tune up'

muscarinic responses". In this respect, the authors were referring to the difference between the receptors found in the CNS and those in other parts of the body.

In fact, we have now found that certain compounds are capable of action at the m1 receptor. In addition, certain compounds are capable of selectively acting as positive allosteric effectors for acetylcholine at the m1 receptors, but not at other receptors.

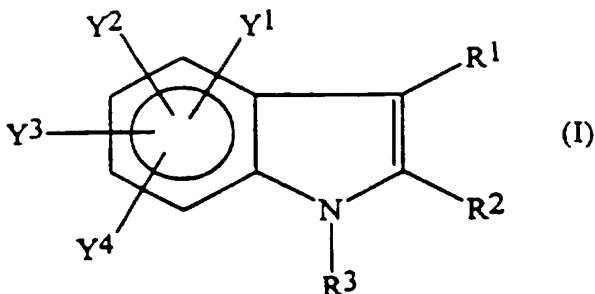
Objects of the Invention

A first object of the invention is to provide compounds which will have an allosteric effect at any of the muscarinic receptors described above.

A second object of the invention is to provide compounds which will have an effect on muscarinic receptors in such a manner as to assist in the prophylaxis and/or treatment of any of the conditions described above, or any condition associated in any way with muscarinic receptors.

Thus, the present invention provides, in a first aspect, a method of regulating m1 receptor response in vivo in a mammalian subject, comprising the step of administering to said subject an effective amount of a selective allosteric effector to regulate said receptor. In a preferred embodiment, the allosteric effector exhibits positive cooperativity with acetylcholine at said receptor.

One class of compounds of the present invention are those compounds of formula (I):



wherein:

Y1, Y2, Y3 and Y4 are the same or different and each represents a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl group, a thiol group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms and substituted with a keto group or at least one substituent α defined below, a haloalkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a group of formula $-(O)_p-B^1-T^1$,

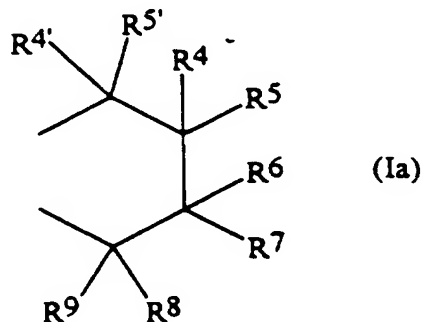
wherein T^1 represents a carboxyl group, a thiocarboxy group, a dithiocarboxy group, a protected carboxyl group, a protected thiocarboxy group, a protected dithiocarboxy group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group, B^1 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α , defined below, and p is 0 or 1;

one of R^1 and R^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group, a substituted aralkyl group, an oxazolyl group, a substituted oxazolyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(A)_p-B^2-T^2$, wherein A represents an oxygen atom or a sulfur atom, T^2 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group, B^2 represents an alkylene group which has from 1 to 6 carbon atoms and which is unsubstituted or has one or more substituents selected from amino groups, protected amino groups, hydroxyl groups, protected hydroxyl groups, oxazolyl groups and substituted oxazolyl groups, and p is as defined above;

and the other of R^1 and R^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group or a substituted aralkyl group;

or

R^1 and R^2 together represent a group of formula (Ia):



[in which R^4 and $R^{4'}$ are the same or different

and each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms;

R^5 and $R^{5'}$ are the same or different and each represents a hydrogen atom or a group of formula $-(O)_p-(CH_2)_n-T^3$ in which T^3 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and $n=0, 1$ or 2 , and p is as defined above;

R^6 represents a hydrogen atom or a hydroxyl group;

R^7 represents a hydrogen atom, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^3-T^4$ in which T^4 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and B^3 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α , and p is as defined above;

R^8 represents a hydrogen atom;

or

when R^9 represents an alkylthio group having from 1 to 6 carbon atoms, R^7 and R^8 together represent a lactone group;

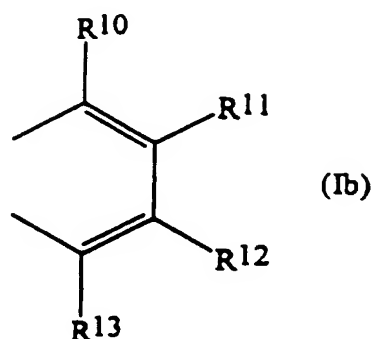
R^9 represents a hydrogen atom or an alkylthio group having from 1 to 6 carbon atoms;

or

R^8 and R^9 together represent an oxo group];

or

R^1 and R^2 together represent a group of formula (Ib):

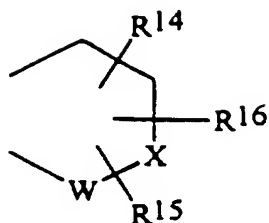


[in which R^{10} , R^{11} , R^{12} and R^{13} are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a hydroxyalkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^4-T^5$

in which T^5 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group, B^4 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α , and, and p is as defined above];

or

R^1 and R^2 together represent a group of formula (Ic):



(Ic)

[in which R^{14} represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a hydroxy-alkyl group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^4-T^5$ in which T^5 , B^4 and p are as defined above; R^{15} and R^{16} are the same or different, and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group; Z is a methylene group, a group of formula $>NH$ or a group of formula $>N-$, and W is a methylene group, a sulfur atom or a group of formula $>S-(O)_q$, where q is 0, 1 or 2, preferably 1 or 2, provided that at least one of W and Z is a methylene group];

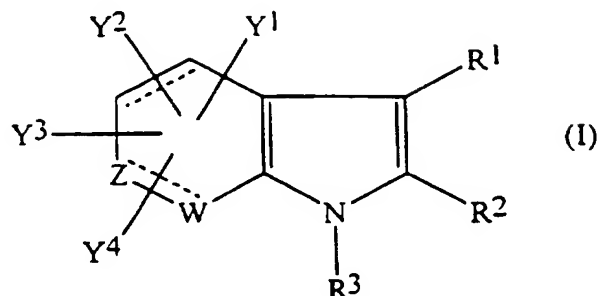
R^3 represents a hydrogen atom or an amino protecting group;

and

said substituents α are hydroxyl groups, aryl groups, aralkyl groups and substituted aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

In a preferred embodiment, there is provided a compound of formula (I):



wherein:

Z represents a methylene group, a methine group, a group of formula $>NH$ or a group of formula $=N-$, and W represents a methylene group, a methine group, a sulfur atom or a group of formula $>S-(O)_v$, where v is 1 or 2, provided that Z does not represent a group of formula $>NH$ when W represents a group of formula $>S-(O)_v$;

each --- represents a single bond or a double bond, provided that when W represents a sulfur atom or a group of formula $>S-(O)_v$, then the --- bond between W and Z represents a single bond;

at least one of Y^1 , Y^2 , Y^3 and Y^4 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a group of formula $-(A)_p-B^1-T^1$,

wherein A represents an oxygen atom or a sulfur atom, T^1 represents a carboxyl group, a thiocarboxy group, a dithiocarboxy group, a protected carboxyl group, a protected thiocarboxy group, a protected dithiocarboxy group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group, B^1 represents a direct bond, an alkylene group

which has from 1 to 4 carbon atoms, or an alkylene group which has from 1 to 4 carbon atoms and which is

substituted by at least one substituent selected from substituents α , defined below, and p is 0 or 1;

any members of the group Y^1 , Y^2 , Y^3 and Y^4 which are not as defined above may be the same or different and each represents a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, a thiol group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms and which is substituted with a keto group or at least one substituent γ defined below, an alkoxy group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkylsulfinyl group having from 1 to 6 carbon atoms, an alkylsulfonyl group having from 1 to 6 carbon atoms, an aryl group, an aralkyloxy group, an aralkylthio group,

and

Y^1 , together with Y^2 , may represent a lactone group or a keto group;

one of R^1 and R^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkanoyl group having from 1 to 6 carbon atoms, an aryl group, an arylcarbonyl group having from 7 to 15 carbon atoms, an aralkyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_q-B^2-T^2$,

wherein T^2 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group, B^2 represents an alkylene group which has from 1

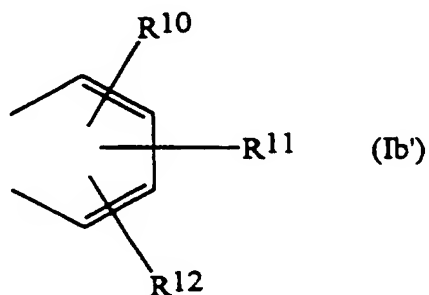
to 6 carbon atoms or an alkylene group which has from 1

to 6 carbon atoms and which has one or more substituents selected from amino groups, protected amino groups, hydroxyl groups and protected hydroxyl groups, and g is 0 or 1;

the other of R^1 and R^2 representing a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group or an aralkyl group,

or

R^1 and R^2 together represent a group of formula (Ib'):



[in which R^{10} , R^{11} and R^{12} are the same or different and each represents a hydrogen atom, a hydroxy group, a halogen atom, a haloalkyl group, an alkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms and having at least one substituent γ defined below, an alkoxy group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkylsulfinyl group having from 1 to 6 carbon atoms or an alkylsulfonyl group having from 1 to 6 carbon atoms];

R^3 represents a hydrogen atom or an amino protecting

group;

said aryl groups being carbocyclic aromatic groups having from 6 to 14 carbon atoms, which may be unsubstituted or substituted with at least one substituent selected from substituents β defined below;

the alkyl parts of said aralkyl groups having from 1 to 3 carbon atoms, the aryl part being as defined above;

substituents α

hydroxyl groups, alkyl groups having from 1 to 6 carbon atoms, alkoxy groups having from 1 to 6 carbon atoms, alkylthio groups having from 1 to 6 carbon atoms, aryl groups as defined above and aralkyl groups as defined above;

substituents β

halogen atoms, nitro groups, hydroxyl groups, amino groups, protected amino groups, alkyl groups having from 1 to 6 carbon atoms, alkoxycarbonyl groups having from 2 to 7 carbon atoms, carboxyl groups, carboxamide groups and aralkoxy groups wherein the aralkyl part is as defined above;

substituents γ

hydroxyl groups, halogen atoms and aryl groups as defined above;

and pharmaceutically acceptable salts and esters thereof.

Other aims, objects, aspects and embodiments of the present invention will become clear as the description progresses.

Detailed Description of the Invention

We prefer that W is a methine group, a methylene group or a sulfur atom, preferably a methine group.

In the compounds of the invention, we prefer that the bonds represented by ... are preferably double bonds.

Preferably, at least one of Y^1 , Y^2 , Y^3 and Y^4 represents a carboxyl group, a sulfonamide group or, preferably, a group of formula $-(A)_p-B^1-T^1$.

A preferably represents an oxygen atom, where it exists.

T^1 preferably represents a carboxyl group, a thiocarboxy group, a dithiocarboxy group or a tetrazolyl group, preferably a carboxyl group or a tetrazolyl group.

B^1 preferably represents an alkylene group which has from 1 to 4 carbon atoms or an alkylene group which has from 1 to 4 carbon atoms and which is substituted by at least one aralkyl group, although we prefer the alkylene group to have 1 or 2 carbon atoms.

We prefer p to be 0.

Where any members of the group Y^1 , Y^2 , Y^3 and Y^4 are not defined above, then we prefer them to be the same or different with each representing a hydrogen atom, a hydroxyl group, a thiol group, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkylsulfinyl group having from 1 to 6 carbon atoms, an alkylsulfonyl group having from 1 to 6 carbon atoms, an aralkyloxy group, an aralkylthio group,

Y^1 , together with Y^2 , optionally representing a keto group. Particularly preferably, the others of the group Y^1 , Y^2 , Y^3 and Y^4 are the same or different with each representing a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms or an alkylthio group having from 1 to 6 carbon atoms.

One of R^1 and R^2 preferably represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group, particularly preferably a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.

The other of R^1 and R^2 preferably represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group, particularly preferably a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.

We particularly prefer that R^1 and R^2 together represent a group of formula (Ia). We also prefer that R^{10} , R^{11} and R^{12} are the same or different and each represents a hydrogen atom, a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms or an alkylthio group having from 1 to 6 carbon atoms.

R^3 preferably represents an aralkyl group, particularly a benzyl or phenethyl group, or a benzyl or phenethyl group substituted with at least one substituent selected from the group consisting of halogen atoms and nitro groups. We especially prefer that R^3 represents an unsubstituted benzyl group.

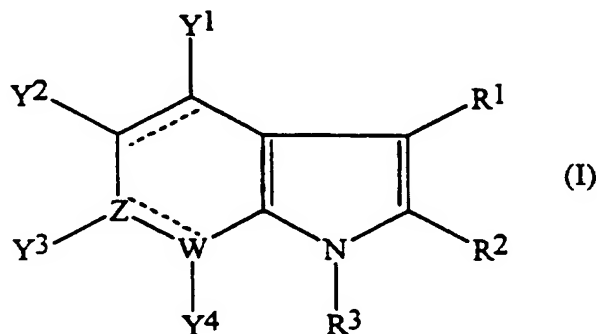
In the compounds of the present invention, we prefer that any aryl groups are selected from carbocyclic

aromatic groups having from 6 to 10 carbon atoms and carbocyclic aromatic groups having from 6 to 10 carbon atoms and which have at least one substituent selected from substituents β , above.

In the compounds of the present invention, we prefer that any aralkyl groups are unsubstituted or substituted with at least one substituent selected from the group consisting of halogen atoms and nitro groups.

In the compounds which follow, it will be appreciated that, as in the compounds above, any preferred restrictions on substituent groups are generally applicable to any compounds of the present invention.

Preferred compounds have the formula (I):



wherein W is -S-, -C--- or is a group of Formula $>S-(O)_v$ where v is 1 or 2;

Z is -C---, >N- or =N-;

the dotted lines individually indicate that the bond to which they are adjacent is a single or a double bond;

Y^1 represents a hydrogen atom, a thiol group, a

hydroxy group, a cyano group, an acetyl group, an alkyl group having from 1 to 6 carbon atoms, a perhaloalkyl group having 1 or 2 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkyl group having 1 or 2 substituents selected from substituents g below, an aralkyl group or an aralkyl group substituted with one or more substituents selected from substituents f below;

Y^2 and Y^3 are the same or different, and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a carboxyl group, an alkylcarbonyl group having from 1 to 6 carbon atoms, a hydroxyl group, an alkoxy group having from 1 to 6 carbon atoms, an alkoxy group substituted with one or more substituents selected from substituents g below, a cyano group, a carbamoyl group, a group of Formula $-\text{CONR}^{30}\text{R}^{31}$, wherein R^{30} and R^{31} are as defined below, an alkylthio group having from 1 to 6 carbon atoms, an alkylthio group substituted with one or more substituents selected from substituents f below or an alkyl group substituted with one or more substituents selected from substituents h below;

Y^4 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms, an aryloxy group, an alkylthio group having from 1 to 6 carbon atoms, a hydroxyl group, a thiol group, a methylsulfonyl group, a methylsulfinyl or an arylthio group;

R^3 represents an alkylcarbonyl group having from 1 to 6 carbon atoms, a hydrogen atom, a methylsulfonyl group, an alkyl group having from 1 to 6 carbon atoms, a benzoyl group, a benzoyl group substituted with one or more substituents selected from substituents f below, an aryl group, an aryl group substituted with one or more substituents selected from substituents f below, an

alkyl group having from 1 to 6 carbon atoms and substituted with one or more substituents selected from substituents h below, an aralkyl group wherein the alkyl part has from 1 to 6 carbon atoms or an aralkyl group wherein the alkyl group has from 1 to 6 carbon atoms and the aryl part is substituted with one or more substituents selected from substituents f below;

R^2 and R^1 are the same or different, and each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms,

or

together, R^1 and R^2 form a phenyl group fused at the bond joining R^2 and R^1 , said phenyl group optionally being substituted with one or more of substituents f below, one of the ring carbon atoms optionally being replaced by a nitrogen atom;

said aryl groups and aryl parts of said aralkyl groups being carbocyclic aromatic groups having from 6 to 14 carbon atoms, which may be unsubstituted or substituted with at least one substituent selected from substituents f defined below;

substituents f

aryloxy groups, nitro groups, halogen atoms, carbamoyl groups, hydroxy groups, alkoxy groups having 1 to 6 carbon atoms, tetrazolyl groups, carboxyl groups and aryl groups;

substituents g

aryl groups, carboxyl groups, cyano groups, hydroxy groups, halogen atoms, thiol groups, amino groups and mono- or di- alkyl amino groups wherein said alkyl groups each have from 1 to 6 carbon atoms, groups of formula $\text{CONR}^{30}\text{R}^{31}$ wherein R^{30} and R^{31} each represents an alkyl group having from 1 to 6 carbon

atoms or, together with the nitrogen to which they are joined form a cyclic or heterocyclic group, or a group of formula $\text{CSNR}^{30}\text{R}^{31}$ where R^{30} and R^{31} are as defined above;

substituents h

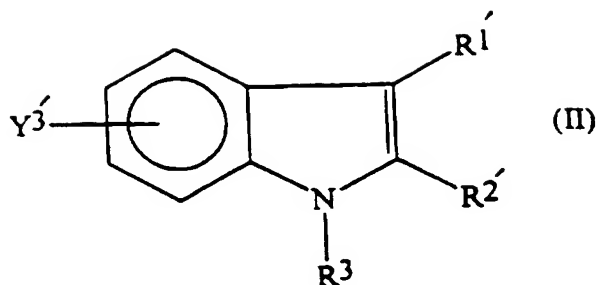
tetrazolyl groups, carboxyl groups, phenyl groups, phenyl substituted with one or more substituents selected from substituents f above, carbamoyl groups, sulfonamide groups, protected sulfonamide groups, carbonylsulfonamide groups, hydroxyl groups, alkoxy groups having 1 to 6 carbon atoms, thiol groups, alkylthio groups having from 1 to 6 carbon atoms, aryl groups, heterocyclic groups, carbonyl groups, thiocarbonyl groups, groups of Formula $\text{CONR}^{30}\text{R}^{31}$ wherein R^{30} and R^{31} each represents an alkyl group having from 1 to 6 carbon atoms or, together with the nitrogen to which they are joined form a cyclic or heterocyclic group, or a group of Formula $\text{CSNR}^{30}\text{R}^{31}$ where R^{30} and R^{31} are as defined above;

PROVIDED THAT not all of Y^1 , Y^2 , Y^3 , Y^4 and R^3 are hydrogen atoms and, when the dotted lines represent single bonds, then any of Y^1 , Y^2 , Y^3 and Y^4 may also represent a keto group and/or any of Y^1 , Y^2 , Y^3 and Y^4 may also represent two such groups Y^1 , Y^2 , Y^3 and Y^4 ,

and pharmaceutically acceptable salts and esters thereof.

In the above formula, it will be appreciated that the substituents Y^1 , Y^2 , Y^3 and Y^4 have been allocated particular positions, which are preferred positions.

Another class of compounds of the present invention are those compounds of formula (II):



wherein:

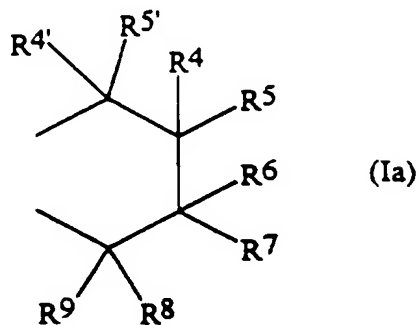
$Y^{3'}$ represents a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group, a substituted aralkyl group, or, when both $R^{1'}$ and $R^{2'}$ are hydrogen atoms, a group of formula -B-T, wherein T represents a carboxyl group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group and B represents an alkylene group having from 1 to 4 carbon atoms and being optionally substituted by a phenyl or benzyl group, said phenyl or benzyl group being optionally substituted by one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

$R^{1'}$ represents a hydrogen atom or a group of formula -B'-T', wherein T' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and B' represents an alkylene group having from 1 to 4 carbon atoms and being optionally substituted by an amino group;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ia):



[in which R^4 and $R^{4'}$ are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms;

R^5 and $R^{5'}$ are the same or different and each represents a hydrogen atom or a group of formula $-(CH_2)_n-T''$ in which T'' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and $n=0, 1$ or 2 ;

R^6 represents a hydrogen atom or a hydroxyl group;

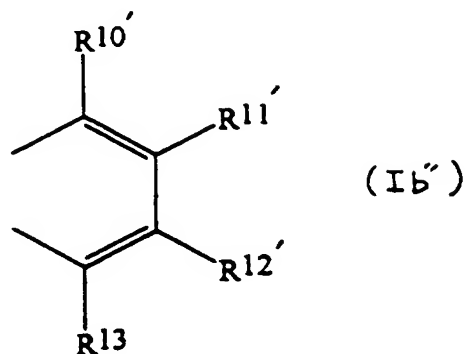
R^7 represents a hydrogen atom or a group of formula $-(CH_2)_m-T'''$ in which T''' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and $m=0, 1$ or 2 ;

R^8 represents a hydrogen atom or, together with R^6 , represents a lactone group;

R^9 represents a hydrogen atom, a keto group or a methylthio group];

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ib''):



[in which $R^{10'}$ represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms;

$R^{11'}$ represents a hydrogen atom or a group of formula $-(CH_2)_n-T''$ in which T'' represents a carboxyl

group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and n is as defined above;

$R^{12'}$ represents a hydrogen atom, a hydroxyl group, a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B''-T'''$ in which T''' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group, $p=0$ or 1 and B'' represents an alkylene group having from 1 to 4 carbon atoms and being optionally substituted by a hydroxyl group, a phenyl group or a benzyl group, said phenyl or benzyl group being

optionally substituted by one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

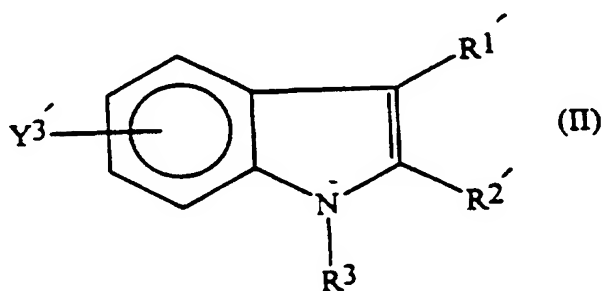
R^{13} represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, or a methylthio group];

and

R^3 represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms substituted with a keto group and/or a phenyl group, said phenyl group being optionally substituted with one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

and pharmaceutically acceptable salts and esters thereof.

Another class of compounds of the present invention are those compounds of formula (II):



wherein:

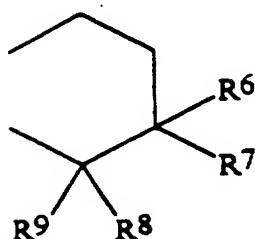
one of $R^{1'}$ and $R^{2'}$ represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl

group, a substituted aryl group, an aralkyl group, a substituted aralkyl group, an oxazolyl group, a substituted oxazolyl group which is substituted by at least one of substituents β , defined below, a group of formula $-(A)_p-B^5-COOH$, where A represents an oxygen atom or a sulfur atom, p is 0 or 1, B^5 represents an alkylene group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from amino groups, protected amino groups, hydroxyl groups, protected hydroxyl groups, oxazolyl groups and substituted oxazolyl groups;

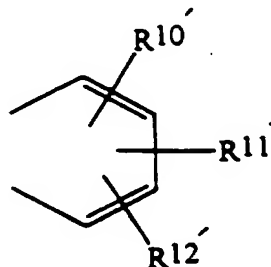
and the other of $R^{1'}$ and $R^{2'}$ represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group, or a substituted aralkyl group;

or

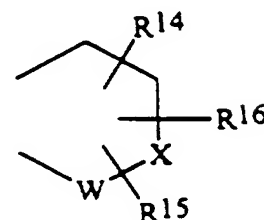
$R^{1'}$ and $R^{2'}$ together represent a group of formula (Id), (Ie) or (Ic):



(Id)



(Ie)



(Ic)

R^{14} and $R^{10'}$ are the same or different and each represents a hydroxy group, a haloalkyl group having from 1 to 6 carbon atoms, a hydroxyalkyl group having from 1 to 6 carbon atoms, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^6-T^6$,

where B^6 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ , defined below, T^6 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group, and p is as defined above;

R^{15} and $R^{12'}$ are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms, or an aryl group;

Z represents a methylene group, a group of formula $>NH$ or a group of formula $>N-$;

W represents a methylene group, a sulfur atom or a group of formula $>S-(O)_q$, wherein q is as defined above;

provided that at least one of W and Z is a methylene group;

$R^{11'}$ represents a hydrogen atom, a haloalkyl group having from 1 to 6 carbon atoms, or an alkylthio group having from 1 to 6 carbon atoms;

R^6 represents a hydroxy group;

R^7 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-B^7-T^7$,

where B^7 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ , defined below, and T^7 represents a carboxyl group, a protected carboxyl group, a sulfonamide

group, a protected sulfonamide group, or a tetrazolyl group;

R⁹ represents a hydrogen atom or an alkylthio group having from 1 to 6 carbon atoms;

or

R⁷ and R⁸ together represent a lactone group, when R⁹ represents an alkylthio group having from 1 to 6 carbon atoms;

or

R⁹ and R⁸ together represent a oxo group;

R³ represents a hydrogen atom or an amino-protecting group;

Y^{3'} represents a hydrogen atom, a halogen atom, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula -B⁸-T⁸,

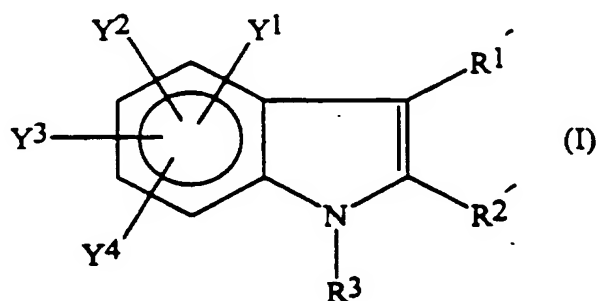
where B⁸ represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ , defined below, and T⁸ represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group;

said substituents β are selected from alkyl groups having from 1 to 6 carbon atoms, aralkyl groups, substituted aralkyl groups, carboxyl groups, nitro groups, halogen atoms and cyano groups;

said substituents γ are selected from hydroxy groups, aralkyl groups, and substituted aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

Another class of compounds of the present invention are those compounds of formula (I):



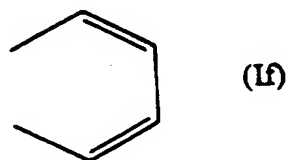
wherein:

$R^{1'}$ represents a hydrogen atom;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (If):



R^3 represents a hydrogen atom, an aralkyl group, an aralkyl group which is substituted by at least one of substituents ϵ , defined below, or an aromatic acyl group;

Y^1 represents a hydrogen atom, a thiol group, an alkyl group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms, a sulfonamide group, a protected sulfonamide group, or a group of formula $-E-COOH$;

Y^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms, a sulfonamide group, a protected sulfonamide group, or a group of formula $-E-COOH$ or $-E-Tet$, where Tet represents a tetrazolyl group;

Y^3 represents a haloalkyl group having from 1 to 6 carbon atoms, a sulfonamide group, a protected sulfonamide group, a group of formula $-E-COOH$ or $-E-Tet$, where Tet is as defined above;

Y^4 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms or a halogen atom; and

E represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ , defined below, or an oxyalkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ , defined below;

PROVIDED that

(1) when $R^{1'}$ and $R^{2'}$ both represent hydrogen atoms, at least one of Y^1 , Y^2 and Y^3 represents a group of formula $-E-COOH$ and R^3 does not represent a hydrogen atom;

(2) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group and R^3 represents a hydrogen atom, Y^1 , Y^2 and Y^4 do not all represent hydrogen atoms;

(3) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group, Y^2 represents a hydrogen atom, and one of Y^1 and Y^4 represents a carboxy group, R^3 does not represent a hydrogen atom;

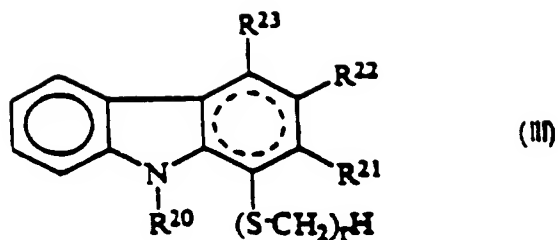
(4) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group, and at least one of Y^1 , Y^2 and Y^4 represents an alkyl group, R^3 does not represent a hydrogen atom;

(5) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group and Y^4 represents a halogen atom, Y^1 and Y^2 do not both represent hydrogen atoms;

said substituents γ are selected from alkyl groups having from 1 to 6 carbon atoms, aralkyl groups, and aralkyl groups substituted by at least one of substituents ϵ , defined below;

said substituents ϵ are selected from halogen atoms and nitro groups.

A most preferred class of compounds of the present invention are those compounds of formula (III):



wherein:

the dotted circle indicates that the ring in which it is present is fully unsaturated;

R^{20} represents a benzyl group optionally substituted with one or more substituents selected from halogen atoms, amino groups, nitro groups and hydroxy groups;

R^{21} represents a group of formula $-Q-Alk-COOH$ wherein Q represents an oxygen atom or a direct bond and Alk represents a lower alkylene group, Alk optionally being substituted with a benzyl group optionally further substituted with one or more substituents selected from halogen atoms, amino groups, nitro groups and hydroxy groups;

R^{22} represents a hydrogen atom;

R^{23} represents a hydrogen atom or a lower alkyl group;
and

$r=0$ or 1 ;

OR

the dotted circle indicates that the core triple ring structure is a 1,2,3,4-tetrahydrocarbazole;

R^{20} , R^{21} and R^{23} all represent hydrogen atoms and R^{22} represents a lower alkyl group substituted with a carboxyl group;

and $r=1$.

In the compounds of formula (III), when the dotted circle indicates that the core triple ring structure is a 1,2,3,4-tetrahydrocarbazole, then we also prefer those compounds wherein $r=0$ for use in the therapeutic indications of the present invention.

In the compounds of formula (III), when R^{20} represents a substituted benzyl group, or Alk is substituted with a substituted benzyl group, then the preferred substituents on said benzyl group are halogen atoms, particularly preferably chlorine, fluorine and bromine atoms, or nitro groups, the preferred number of substituents being 0 or 1.

In the compounds of formula (III), Alk is preferably a methylene, ethylene or propylene group, particularly preferably an ethylene group, and Z is preferably a carbon-carbon single bond.

In the compounds of formula (III), R^{23} preferably represents a hydrogen atom or a methyl group, preferably a hydrogen atom.

The present invention also provides the above classes of compounds for use in the treatment of dementia.

The present invention also provides the above classes of compounds for use in the treatment of Alzheimer's disease and delirium and as sedatives for the central nervous system.

The present invention still further provides the above classes of compounds for use in the manufacture of a medicament for the treatment of Alzheimer's disease.

The invention also embraces those compounds among those described above which are novel.

In the compounds of the present invention, where Y^1 , Y^2 , Y^3 , Y^4 , Y , R^3 , R^{12} , B , B'' , substituent ϵ or substituent β represents a halogen atom, this may be a fluorine, chlorine, bromine or iodine atom and is preferably a fluorine or chlorine atom.

Where Y^1 , Y^2 , Y^3 , Y^4 , Y , R^1 , R^2 , R^3 , R^4 , $R^{4'}$, R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , substituent β or substituent γ represents an alkyl group having from 1 to 6 carbon atoms, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, hexyl and isohexyl groups. Of these, we prefer those alkyl groups having from 1 to 4 carbon atoms, preferably the methyl, ethyl, propyl, isopropyl, butyl and isobutyl groups, and most preferably the methyl group.

Where $Y^1, Y^2, Y^3, Y^4, Y, R^9, R^{10}, R^{11}, R^{12}$ or R^{13} represents an alkylthio group having from 1 to 6 carbon atoms, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, t-butylthio, pentylthio, isopentylthio, neopentylthio, 2-methylbutylthio, 1-ethylpropylthio, 4-methylpentylthio, 3-methylpentylthio, 2-methylpentylthio, 1-methylpentylthio, 3,3-dimethylbutylthio, 2,2-dimethylbutylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,3-dimethylbutylthio, 2-ethylbutylthio, hexylthio and isohexylthio groups. Of these, we prefer those alkylthio groups having from 1 to 4 carbon atoms, preferably the methylthio, ethylthio, propylthio, isopropylthio, butylthio and isobutylthio groups, and most preferably the methylthio group.

Where $Y^1, Y^2, Y^3, Y^4, T, T^1, T^2, T^3, T^4, T^5, T^6, T^7, T^8, R^1, R^7, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}$ represents a protected carboxy group, there is no particular restriction on the nature of the carboxy-protecting group used, and any carboxy-protecting group known in the art may equally be used in this reaction. Non-limiting examples of such groups include:

alkyl groups having from 1 to 25 carbon atoms, more preferably from 1 to 6 carbon atoms, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, hexyl, isohexyl,

heptyl, octyl, nonyl, decyl, dodecyl, tridecyl, pentadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl, tricosyl, tetracosyl and pentacosyl groups, but most preferably the methyl, ethyl and t-butyl groups;

cycloalkyl groups having from 3 to 7 carbon atoms, for example the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups;

aralkyl groups, in which the alkyl part has from 1 to 3 carbon atoms and the aryl part is a carbocyclic aromatic group having from 6 to 14 carbon atoms, which may be substituted or unsubstituted and, if substituted, has at least one of substituents β defined and exemplified above, although the unsubstituted groups are preferred; examples of such aralkyl groups include the benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)-ethyl, 2-(2-naphthyl)ethyl, benzhydryl (i.e. diphenylmethyl), triphenylmethyl, bis(o-nitrophenyl)methyl, 9-anthrylmethyl, 2,4,6-trimethylbenzyl, 4-bromobenzyl, 2-nitrobenzyl, 4-nitrobenzyl, 3-nitrobenzyl, 4-methoxybenzyl and piperonyl groups;

alkenyl groups having from 2 to 6 carbon atoms, such as the vinyl, allyl, 2-methylallyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl groups, of which the vinyl, allyl, 2-methylallyl, 1-propenyl, isopropenyl and butenyl groups are preferred, the allyl and 2-methylallyl groups being most preferred;

haloalkyl groups having from 1 to 6, preferably from

1 to 4, carbon atoms, in which the alkyl part is as defined and exemplified in relation to the alkyl groups above, and the halogen atom is chlorine, fluorine, bromine or iodine, such as the 2,2,2-trichloroethyl, 2-haloethyl (e.g. 2-chloroethyl, 2-fluoroethyl, 2-bromoethyl or 2-iodoethyl), 2,2-dibromoethyl and 2,2,2-tribromoethyl groups;

substituted silylalkyl groups, in which the alkyl part is as defined and exemplified above, and the silyl group has up to 3 substituents selected from alkyl groups having from 1 to 6 carbon atoms and phenyl groups which are unsubstituted or have at least one substituent selected from substituents β defined and exemplified above, for example a 2-trimethylsilylethyl group;

phenyl groups, in which the phenyl group is unsubstituted or substituted, preferably with at least one alkyl group having from 1 to 4 carbon atoms or acylamino group, for example the phenyl, tolyl and benzamidophenyl groups;

phenacyl groups, which may be unsubstituted or have at least one of substituents β defined and exemplified above, for example the phenacyl group itself or the *p*-bromophenacyl group;

cyclic and acyclic terpenyl groups, for example the geranyl, neryl, linalyl, phytyl, menthyl (especially *m*- and *p*-menthyl), thujyl, caryl, pinanyl, bornyl, norcaryl, norpinanyl, norbornyl, menthenyl, camphenyl and norbornenyl groups;

alkoxymethyl groups, in which the alkoxy part has from 1 to 6, preferably from 1 to 4, carbon atoms and may itself be substituted by a single

unsubstituted alkoxy group, such as the methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl and methoxyethoxymethyl groups;

aliphatic acyloxyalkyl groups, in which the acyl group is preferably an alkanoyl group and is more preferably an alkanoyl group having from 2 to 6 carbon atoms, and the alkyl part has from 1 to 6, and preferably from 1 to 4, carbon atoms such as the acetoxymethyl, propionyloxymethyl, butyryloxymethyl, isobutyryloxymethyl, pivaloyloxymethyl, 1-pivaloyloxyethyl, 1-acetoxyethyl, 1-isobutyryloxyethyl, 1-pivaloyloxypropyl, 2-methyl-1-pivaloyloxypropyl, 2-pivaloyloxypropyl, 1-isobutyryloxyethyl, 1-isobutyryloxypropyl, 1-acetoxypropyl, 1-acetoxy-2-methylpropyl, 1-propionyloxyethyl, 1-propionyloxypropyl, 2-acetoxypropyl and 1-butyryloxyethyl groups;

cycloalkyl-substituted aliphatic acyloxyalkyl groups, in which the acyl group is preferably an alkanoyl group and is more preferably an alkanoyl group having from 2 to 6 carbon atoms, the cycloalkyl substituent has from 3 to 7 carbon atoms, and the alkyl part has from 1 to 6, preferably from 1 to 4, carbon atoms, such as the (cyclohexylacetoxymethyl, 1-(cyclohexylacetoxymethyl, 1-(cyclohexylacetoxymethyl, 2-methyl-1-(cyclohexylacetoxymethyl, (cyclopentylacetoxymethyl, 1-(cyclopentylacetoxymethyl, 1-(cyclopentylacetoxymethyl, 1-(cyclopentylacetoxymethyl, 2-methyl-1-(cyclopentylacetoxymethyl, groups;

alkoxycarbonyloxyalkyl groups, especially 1-(alkoxycarbonyloxy)ethyl groups, in which the alkoxy part has from 1 to 10, preferably from 1 to 6, and more preferably from 1 to 4, carbon atoms,

and the alkyl part has from 1 to 6, preferably from 1 to 4, carbon atoms, such as the 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl, 1-propoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl, 1-butoxycarbonyloxyethyl, 1-isobutoxycarbonyloxyethyl, 1-sec-butoxycarbonyloxyethyl, 1-t-butoxycarbonyloxyethyl, 1-(1-ethylpropoxycarbonyloxy)ethyl and 1-(1,1-dipropylbutoxycarbonyloxy)ethyl groups, and other alkoxycarbonylalkyl groups, in which both the alkoxy and alkyl groups have from 1 to 6, preferably from 1 to 4, carbon atoms, such as the 2-methyl-1-(isopropoxycarbonyloxy)propyl, 2-(isopropoxycarbonyloxy)propyl, isopropoxycarbonyloxymethyl, t-butoxycarbonyloxymethyl, methoxycarbonyloxymethyl and ethoxycarbonyloxymethyl groups;

cycloalkylcarbonyloxyalkyl and cycloalkyloxy-carbonyloxyalkyl groups, in which the cycloalkyl group has from 3 to 10, preferably from 3 to 7, carbon atoms, is mono- or poly- cyclic and is optionally substituted by at least one (and preferably only one) alkyl group having from 1 to 4 carbon atoms (e.g. selected from those alkyl groups exemplified above) and the alkyl part has from 1 to 6, more preferably from 1 to 4, carbon atoms (e.g. selected from those alkyl groups exemplified above) and is most preferably methyl, ethyl or propyl, for example the 1-methylcyclohexylcarbonyloxymethyl, 1-methylcyclohexyloxy-carbonyloxymethyl, cyclopentyl-oxy-carbonyloxymethyl, cyclopentylcarbonyloxymethyl, 1-cyclohexyloxy-carbonyloxyethyl, 1-cyclohexyl-carbonyloxyethyl, 1-cyclopentyloxy-carbonyloxyethyl, 1-cyclopentylcarbonyloxyethyl, 1-cycloheptyloxy-carbonyloxyethyl, 1-cycloheptylcarbonyloxyethyl, 1-methylcyclopentylcarbonyloxymethyl, 1-methylcyclopentyloxy-carbonyloxymethyl, 2-methyl-1-(1-methylcyclohexylcarbonyloxy)propyl, 1-(1-methylcyclo-

hexylcarbonyloxy)propyl, 2-(1-methylcyclohexylcarbonyloxy)propyl, 1-(cyclohexylcarbonyloxy)propyl, 2-(cyclohexylcarbonyloxy)propyl, 2-methyl-1-(1-methylcyclopentylcarbonyloxy)propyl, 1-(1-methylcyclopentylcarbonyloxy)propyl, 2-(1-methylcyclopentylcarbonyloxy)propyl, 1-(cyclopentylcarbonyloxy)propyl, 2-(cyclopentylcarbonyloxy)propyl, 1-(1-methylcyclopentylcarbonyloxy)ethyl, 1-(1-methylcyclopentylcarbonyloxy)propyl, adamantyl-oxy-carbonyloxymethyl, adamantylcarbonyloxymethyl, 1-adamantyloxy-carbonyloxyethyl and 1-adamantylcarbonyloxyethyl groups;

cycloalkylalkoxy-carbonyloxyalkyl groups in which the alkoxy group has a single cycloalkyl substituent, the cycloalkyl substituent having from 3 to 10, preferably from 3 to 7, carbon atoms and mono- or poly- cyclic, for example the cyclopropylmethoxy-carbonyloxymethyl, cyclobutylmethoxy-carbonyloxymethyl, cyclopentylmethoxy-carbonyloxymethyl, cyclohexylmethoxy-carbonyloxymethyl, 1-(cyclopropylmethoxy-carbonyloxy)ethyl, 1-(cyclobutylmethoxy-carbonyloxy)ethyl, 1-(cyclopentylmethoxy-carbonyloxy)ethyl and 1-(cyclohexylmethoxy-carbonyloxy)ethyl groups;

terpenylcarbonyloxyalkyl and terpenyloxy-carbonyloxyalkyl groups, in which the terpenyl group is as exemplified above, and is preferably a cyclic terpenyl group, for example the 1-(menthyloxy-carbonyloxy)ethyl, 1-(menthylcarbonyloxy)ethyl, menthyloxy-carbonyloxymethyl, menthylcarbonyloxy-methyl, 1-(3-pinanyloxy-carbonyloxy)ethyl, 1-(3-pinanylcarbonyloxy)ethyl, 3-pinanyloxy-carbonyloxymethyl and 3-pinanylcarbonyloxymethyl groups;

5-alkyl or 5-phenyl [which may be substituted by at

least one of substituents β , defined and exemplified above] (2-oxo-1,3-dioxolen-4-yl)alkyl groups in which each alkyl group (which may be the same or different) has from 1 to 6, preferably from 1 to 4, carbon atoms, for example the (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-isopropyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and 1-(5-methyl-2-oxo-1,3-dioxolen-4-yl)ethyl groups; and

other groups, such as the phthalidyl, indanyl and 2-oxo-4,5,6,7-tetrahydro-1,3-benzodioxolen-4-yl groups.

Where T, T¹, T², T³, T⁴, T⁵, T⁶, T⁷, T⁸, T', T'', T''', T'''' or Tet represents a tetrazolyl group, this is preferably a tetrazol-5-yl group.

Where R¹, B² or B⁵ represents an oxazolyl group, this is preferably an oxazol-5-yl group, which may be substituted or unsubstituted. In the case of substituents on the carbon atom, these may be selected from alkyl groups having from 1 to 6 carbon atoms (such as those exemplified above), and aralkyl and acyl groups (such as those exemplified below), as well as nitro groups, halogen atoms and cyano groups.

Where B¹ B² B³ B⁴, B⁵ B⁶ B⁷ B⁸, B, B', B'' or E represents an alkylene group, this may be a straight or branched chain alkylene group having from 1 to 3 or from 1 to 4 carbon atoms. Examples of such groups include the methylene, ethylene, ethylidene, trimethylene, propylene, propylidene, isopropylidene, tetramethylene, butylidene, 1-methylethylene, 2-methylethylene, 1-methyltrimethylene, 2-methyltrimethylene, 3-methyl-

trimethylene, pentamethylene and hexamethylene groups, of which the methylene and ethylene groups are preferred.

Where E represents an oxyalkylene group, this may be a straight or branched chain oxyalkylene group having from 1 to 3 or from 1 to 4 carbon atoms. Examples of such groups include the oxymethylene, oxyethylene, oxytrimethylene, oxypropylene, oxytetramethylene, 1-methyloxyethylene, 2-methyloxyethylene, 1-methyl-oxytrimethylene, 2-methyloxytrimethylene and 3-methyl-oxytrimethylene groups, of which the oxymethylene and oxyethylene groups are preferred.

Where the alkylene group represented by B² or B⁵ is substituted by a protected amino group or where R³ or R¹³ represents an amino-protecting group, the protecting group used is not critical to the present invention, and any protecting group used in compounds of this type may equally be used here. Examples of suitable protecting groups include: acyl groups, such as the lower aliphatic carboxylic acyl, preferably alkanoyl and particularly alkanoyl groups having from 1 to 6 carbon atoms; or aromatic carboxylic acyl groups, preferably arylcarbonyl groups in which the aryl moiety is as defined and exemplified below in relation to R¹, R², R¹², R¹⁵, Y or substituent α, for example: aliphatic lower acyl groups such as the formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl and pivaloyl groups; and aromatic acyl groups, such as the benzoyl, 4-acetoxybenzoyl, 4-methoxybenzoyl, 3-methoxybenzoyl, 2-methoxybenzoyl, 4-methylbenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 3,4-dichlorobenzoyl, 3,4-difluorobenzoyl, 3,4-dimethoxybenzoyl, 4-nitrobenzoyl, 4-aminobenzoyl, 4-acetamidobenzoyl and 1-naphthoyl groups. Of these, we prefer the acetyl, benzoyl and isobutyryl groups.

The aromatic acyl groups represented by R^3 in one embodiment of the present invention may also be as defined and exemplified above.

Where R^1 , R^2 , R^{12} , R^{15} , Y or substituent α is an aryl group, this has from 6 to 14 carbon atoms, more preferably from 6 to 10, and most preferably 6 or 10, carbon atoms, in one or more, preferably one, two or three, and more preferably one, carbocyclic ring, and examples of the unsubstituted groups include the phenyl, 1-naphthyl, 2-naphthyl, indenyl, acenaphthenyl, anthryl and phenanthryl groups, preferably the phenyl or naphthyl (1- or 2- naphthyl) group, and more preferably the phenyl group. Such groups may be unsubstituted or they may have on the ring at least one substituent, preferably from 1 to 3 substituents, selected from the group consisting of substituents ψ , defined and exemplified below. Examples of such substituted groups include the phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl and 4-chlorophenyl groups. However, the unsubstituted groups, especially the phenyl group, are preferred.

Examples of substituents ψ include:

alkyl groups having from 1 to 4 carbon atoms, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and t-butyl groups, of which the methyl, ethyl, propyl and isopropyl groups are preferred;

alkoxy groups having from 1 to 4 carbon atoms, such as the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and t-butoxy groups, of which

the methoxy and ethoxy groups are preferred; and

halogen atoms, such as the fluorine, chlorine, bromine and iodine atoms, of which the fluorine, chlorine and bromine atoms are preferred; and

nitro groups.

Where R^1 , R^2 , R^3 , γ , substituent α , substituent β or substituent γ is an aralkyl group, this may be an alkyl group having from 1 to 4 carbon atoms which is substituted by at least one, and preferably from 1 to 3, more preferably 1 or 2, and most preferably one, aryl group, which may be any of the aryl groups defined and exemplified above. Examples of the alkyl groups so substituted include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl and sec-butyl groups. Examples of preferred aralkyl groups include the benzyl, 1-phenylethyl, 2-phenylethyl (= phenethyl), 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 4-phenylbutyl, 2-methyl-2-phenylethyl, 1-methyl-2-phenylethyl, 1-naphthylmethyl, 2-naphthylmethyl, indenylmethyl, acenaphthenylmethyl, anthrylmethyl, phenanthrylmethyl, benzhydryl and trityl (= triphenylmethyl) groups, preferably the benzyl or naphthylmethyl (1- or 2- naphthylmethyl) group, and more preferably the benzyl group. Such groups may be unsubstituted or they may have on the ring at least one substituent, preferably 1 to 3 substituents, selected from the group consisting of substituents ψ , defined and exemplified above. Examples of such substituted groups include the benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-nitrobenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl and 4-chlorobenzyl groups. However, the

unsubstituted groups, especially the benzyl group, are preferred.

Where R^7 and R^8 or R^8 and R^6 represents a lactone group, this is a group containing $-O-C(O)-$, and optionally one or more methylene groups, i.e. $-(CH_2)_s-O-C(O)-(CH_2)_t-$, where s and t are the same or different and each is 0 or an integer from 1 to 3, preferably 1 or 2, provided that $(s + t)$ is not greater than 5.

Where R^{10} , R^{11} , R^{12} , R^{13} or R^{14} represents a hydroxyalkyl group having from 1 to 6 carbon atoms, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the hydroxymethyl, 1- or 2- hydroxyethyl, 1-, 2- or 3- hydroxypropyl, 1- or 2- hydroxy-2-methylethyl, 1-, 2-, 3- or 4- hydroxybutyl, 1-, 2-, 3-, 4- or 5- hydroxypentyl or 1-, 2-, 3-, 4-, 5- or 6- hydroxyhexyl groups. Of these, we prefer those hydroxyalkyl groups having from 1 to 4 carbon atoms, preferably the hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl and 4-hydroxybutyl groups, and most preferably the hydroxymethyl group.

Where Y^1 , Y^2 , Y^3 , Y^4 , R^{10} , R^{11} , R^{12} , R^{14} or R^{15} represents a haloalkyl group, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, in which the alkyl part is as defined and exemplified in relation to the alkyl groups above, and the halogen atom is chlorine, fluorine, bromine or iodine, such as the trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl, difluoromethyl, dichloromethyl, dibromomethyl, diiodomethyl, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2-haloethyl (e.g. 2-chloroethyl,

2-fluoroethyl, 2-bromoethyl or 2-iodoethyl), 2,2-dibromoethyl, 2,2,2-tribromoethyl, 3-fluoropropyl, 4-fluorobutyl, 5-fluoropentyl, 6-fluorohexyl, 3-chloropropyl, 4-chlorobutyl, 5-chloropentyl, 6-chlorohexyl and groups;

Where B² or B⁵ is substituted by a protected hydroxyl group, then there is no particular restriction on the nature of the hydroxy-protecting group used, and any hydroxy-protecting group known in the art may be employed. Suitable groups include protecting groups capable of being cleaved by chemical methods (such as hydrogenolysis, hydrolysis, electrolysis or photolysis) to generate a free hydroxy group, and protecting groups capable of being cleaved in vivo by biological methods, such as hydrolysis.

Suitable examples of hydroxy-protecting groups which may be cleaved by chemical means include: aliphatic acyl groups, preferably alkanoyl groups having from 1 to 25 carbon atoms, more preferably from 1 to 20 carbon atoms, still more preferably from 1 to 6 carbon atoms, and most preferably from 1 to 4 carbon atoms (such as formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, isovaleryl, hexanoyl, heptanoyl, octanoyl, lauroyl, myristoyl, tridecanoyl, palmitoyl and stearoyl groups, of which the acetyl group is most preferred); halogenated alkanoyl groups having from 2 to 6 carbon atoms, especially halogenated acetyl groups (such as the chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl groups); lower alkoxyalkanoyl groups in which the alkoxy part has from 1 to 6, preferably from 1 to 3, carbon atoms and the alkanoyl part has from 2 to 6 carbon atoms and is preferably an acetyl group (such as the methoxyacetyl group);

unsaturated analogues of the above groups, especially alkenoyl or alkynoyl groups having from 3 to 6 carbon atoms [such as the acryloyl, methacryloyl, propioloyl, crotonoyl, isocrotonoyl and (*E*)-2-methyl-2-butenoyl groups];

aromatic acyl groups, preferably arylcarbonyl groups, in which the aryl part has from 6 to 14, more preferably from 6 to 10, and most preferably 6, ring carbon atoms and is a carbocyclic group, which is unsubstituted or has from 1 to 5, preferably from 1 to 3 substituents, selected from the group consisting of substituents ψ , defined and exemplified above, said aromatic acyl groups including, for example,

unsubstituted groups (such as the benzoyl, α -naphthoyl and β -naphthoyl groups); halogenated arylcarbonyl groups (such as the 2-bromobenzoyl and 4-chlorobenzoyl groups); lower alkyl-substituted arylcarbonyl groups, in which the or each alkyl substituent has from 1 to 6, preferably from 1 to 4, carbon atoms (such as the 2,4,6-trimethylbenzoyl and 4-toluoyl groups); lower alkoxy-substituted arylcarbonyl groups, in which the or each alkoxy substituent preferably has from 1 to 6, more preferably from 1 to 4, carbon atoms (such as the 4-anisoyl group); carboxy-substituted arylcarbonyl groups (such as the 2-carboxybenzoyl, 3-carboxybenzoyl and 4-carboxybenzoyl groups); nitro-substituted arylcarbonyl groups (such as the 4-nitrobenzoyl and 2-nitrobenzoyl groups); lower alkoxycarbonyl-substituted arylcarbonyl groups, in which the or each alkoxycarbonyl substituent preferably has from 2 to 6 carbon atoms [such as the 2-(methoxycarbonyl)benzoyl group]; and aryl-substituted arylcarbonyl groups, in which the aryl substituent is as defined above, except that, if it is substituted by a further aryl group, that aryl group is not itself substituted by an aryl group

(such as the 4-phenylbenzoyl group); heterocyclic groups having 5 or 6 ring atoms, of which 1 or 2 are hetero-atoms selected from the group consisting of oxygen, sulfur and nitrogen atoms, preferably oxygen or sulfur atoms, which groups may be unsubstituted or may have at least one substituent selected from the group consisting of substituents ψ and oxygen atoms, preferably halogen atoms and alkoxy groups, and wherein suitable examples of said heterocyclic groups include:

the tetrahydropyranyl groups, which may be substituted or unsubstituted, such as the tetrahydropyran-2-yl, 3-bromotetrahydropyran-2-yl and 4-methoxytetrahydropyran-4-yl groups, tetrahydrothiopyranyl groups, which may be substituted or unsubstituted, such as the tetrahydrothiopyran-2-yl and 4-methoxytetrahydrothiopyran-4-yl groups; tetrahydrofuran-yl groups and tetrahydrothienyl groups, which may be substituted or unsubstituted, such as the tetrahydrofuran-2-yl group and tetrahydrothien-2-yl group;

tri-substituted silyl groups, in which all three or two or one of the substituents are alkyl groups having from 1 to 5, preferably from 1 to 4, carbon atoms, and none, one or two of the substituents are aryl groups, as defined above, but preferably phenyl or substituted phenyl groups, preferably: tri(loweralkyl)silyl groups, such as the trimethylsilyl, triethylsilyl, isopropyl-dimethylsilyl, t-butyl-dimethylsilyl, methyl-diisopropylsilyl, methyl-di-t-butylsilyl and triisopropylsilyl groups; and tri(lower alkyl)silyl groups in which one or two of the alkyl groups have been replaced by aryl groups, such as the diphenylmethylsilyl, diphenylbutylsilyl, diphenyl-t-butylsilyl, diphenylisopropylsilyl and phenyl-diisopropylsilyl groups;

alkoxyalkyl groups, in which the alkoxy and alkyl parts each have from 1 to 6, preferably from 1 to 4, carbon atoms, especially alkoxymethyl groups, and such groups

which have at least one, preferably from 1 to 5, more preferably from 1 to 3, and most preferably 1, substituents, preferably: lower alkoxyethyl groups and other alkoxyalkyl groups (such as the methoxyethyl, ethoxyethyl, propoxyethyl, isopropoxyethyl, butoxyethyl and t-butoxyethyl groups); lower alkoxy-substituted lower alkoxyethyl groups (such as the 2-methoxyethoxyethyl group); halogenated lower alkoxyethyl groups [such as the 2,2,2-trichloroethoxyethyl and bis(2-chloroethoxy)ethyl groups] and lower alkoxy-substituted ethyl groups (such as the 1-ethoxyethyl, 1-methyl-1-methoxyethyl and 1-isopropoxyethyl groups);

other substituted ethyl groups, preferably: halogenated ethyl groups (such as the 2,2,2-trichloroethyl group); and arylselenyl-substituted ethyl groups, in which the aryl part is as defined above, such as the 2-(phenylselenyl)ethyl group;

aryl groups, preferably alkyl groups, having from 1 to 4, more preferably from 1 to 3, and most preferably 1 or 2, carbon atoms which are substituted with from 1 to 3 aryl groups, as defined and exemplified above, which may be unsubstituted (such as the benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, α -naphthylethyl, β -naphthylethyl, diphenylethyl, triphenylethyl, α -naphthylmethyl and 9-anthrylmethyl groups) or substituted on the aryl part with a lower alkyl group, a lower alkoxy group, a nitro group, a halogen atom, a cyano group, or an alkylenedioxy group having from 1 to 3 carbon atoms, preferably a methylenedioxy group, examples including:

the 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenyldiphenylethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzoyl, 4-bromobenzyl, 4-cyanobenzyl, 4-cyanobenzyldiphenylethyl, bis(2-nitrophenyl)methyl and piperonyl groups;

alkoxycarbonyl groups, especially such groups having from 2 to 7, more preferably 2 to 5, carbon atoms and which may be unsubstituted (such as the methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl and isobutoxycarbonyl groups) or substituted with a halogen atom or a tri-substituted silyl group, for example, a tri(lower alkylsilyl) group (such as the 2,2,2-trichloroethoxycarbonyl and 2-trimethylsilylethoxycarbonyl groups); alkenyloxycarbonyl groups in which the alkenyl part has from 2 to 6, preferably from 2 to 4, carbon atoms (such as the vinyloxycarbonyl and allyloxycarbonyl groups); sulfo groups; and aralkyloxycarbonyl groups, in which the aralkyl part is as defined and exemplified above, and in which the aryl ring, if substituted, is substituted by at least one substituent selected from the group consisting of substituents ψ , defined and exemplified above, one or two lower alkoxy or nitro substituents, such as one of the benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl groups.

Examples of hydroxy-protecting groups which are capable of being cleaved in vivo by biological methods such as enzymatic hydrolysis include: acyloxyalkyl groups, in which the alkyl part has from 1 to 6 carbon atoms, such as the acetoxymethyl, dimethylaminoacetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl and 1-acetoxyethyl groups; 1-(alkoxycarbonyloxy)alkyl groups, in which each of the alkoxy and alkyl parts has from 1 to 6 carbon atoms, such as the methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, propoxycarbonyloxymethyl, isopropoxycarbonyloxymethyl, butoxycarbonyloxymethyl, isobutoxycarbonyloxymethyl, cyclohexyloxycarbonyloxymethyl, cyclohexyloxycarbonyloxycyclohexylmethyl, 1-methoxycarbonyloxyethyl,

1-ethoxycarbonyloxyethyl, 1-propoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl, 1-butoxycarbonyloxyethyl, 1-isobutoxycarbonyloxyethyl, 1-t-butoxycarbonyloxyethyl, 1-cyclohexyloxycarbonyloxyethyl and 1-ethoxycarbonyloxy-propyl groups;
carbonyloxyalkyl groups, including oxodioxolenylmethyl groups, such as the 4-methyloxodioxolenylmethyl, 4-phenyl-4-oxodioxolenylmethyl and oxodioxolenylmethyl groups;
dioxolenylalkyl groups, aliphatic acyl groups and aromatic acyl groups;
any residue which forms a salt of a half-ester of a dicarboxylic acid, such as succinic acid;
any residue which forms a salt of a phosphate;
a residue of an ester of an amino acid; and
carbonyloxyalkyloxycarbonyl groups, such as the pivaloyloxymethoxycarbonyl group.

Of the above, we prefer the aliphatic acyl groups, tri-substituted silyl groups, and most preferably the tri-substituted silyl groups.

Where $Y^1, Y^2, Y^3, Y^4, T^1, T^2, T^3, T^4, T^5, T^6, T^7, T^8, R^1, R^2, R^7, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, T, T', T'', T''', T''''$ or T'''' represents a protected sulfonamide group, there is no particular restriction on the nature of the sulfonamide-protecting group used, and any sulfonamide protecting group known in the art may equally be used here.

Non-limiting examples of suitable protecting groups for sulfonamides include: acyl groups, which may be unsubstituted or substituted by at least one (and preferably only one) aryl groups having from 6 to 14 carbon atoms (most preferably phenyl), such as the lower aliphatic acyl or aromatic acyl groups, for example;

aliphatic lower acyl groups such as the formyl, acetyl, phenylacetyl, diphenylacetyl, propionyl, 3-phenylpropionyl, butyryl, isobutyryl, valeryl, isovaleryl and pivaloyl groups; and aromatic acyl groups, such as the benzoyl, 4-acetoxybenzoyl, 4-methoxybenzoyl, 3-methoxybenzoyl, 2-methoxybenzoyl, 4-methylbenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 3,4-dichlorobenzoyl, 3,4-difluorobenzoyl, 3,4-dimethylbenzoyl, 4-nitrobenzoyl, 4-aminobenzoyl, 4-acetamidobenzoyl, 4-phenylbenzoyl and 1-naphthoyl groups. Of these, we prefer the acetyl, phenylacetyl, benzoyl and isobutyryl groups, most preferably the phenylacetyl group.

Where the compound of the present invention contains a carboxyl group, it may form esters. Examples of groups with which such compounds may form esters include the carboxy-protecting groups listed above. In most cases, we prefer to administer the compound as the free acid; however, where the compound is to be administered as an ester, we prefer that the ester group should be one of those groups which can be removed easily in vivo, and most preferably the aliphatic acyloxyalkyl groups, alkoxycarbonyloxyalkyl groups, cycloalkylcarbonyloxyalkyl groups, phthalidyl groups and (5-substituted 2-oxo-1,3-dioxolen-4-yl)methyl groups.

Those compounds of the present invention which contain a carboxyl group can form salts. Examples of such salts include: salts with an alkali metal, such as sodium, potassium or lithium; salts with an alkaline earth metal, such as barium or calcium; salts with another metal, such as magnesium or aluminum; ammonium salts; organic base salts, such as a salt with triethylamine, diisopropylamine, cyclohexylamine or dicyclohexylamine; and salts with a basic amino acid, such as lysine or arginine. Also, where the compound of

the present invention contains a basic group in its molecule, it can form acid addition salts. Examples of such acid addition salts include: salts with mineral acids, especially hydrohalic acids (such as hydrofluoric acid, hydrobromic acid, hydroiodic acid or hydrochloric acid), nitric acid, carbonic acid, sulfuric acid or phosphoric acid; salts with lower alkylsulfonic acids, such as methanesulfonic acid, trifluoromethanesulfonic acid or ethanesulfonic acid; salts with arylsulfonic acids, such as benzenesulfonic acid or p-toluenesulfonic acid; salts with organic carboxylic acids, such as acetic acid, fumaric acid, tartaric acid, oxalic acid, maleic acid, malic acid, succinic acid, benzoic acid, mandelic acid, ascorbic acid, lactic acid, gluconic acid or citric acid; and salts with amino acids, such as glutamic acid or aspartic acid.

A preferred class of compounds of the present invention are those compounds of formula (I), in which:

Y^1 , Y^2 and Y^4 each represents a hydrogen atom;

Y^3 represents a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a carboxyl group, a protected carboxyl group or a group of formula $-(O)_p-B^1-T^1$,

wherein T^1 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group, B^1 represents an alkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α , defined below, and p is 0 or 1;

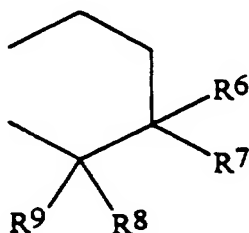
$R^{1'}$ represents a hydrogen atom, a carboxyl group, a

protected carboxyl group, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group, a substituted aralkyl group or a group of formula $-B^2-COOH$, wherein T^2 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group, B^2 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by an amino group or a protected amino group;

$R^{2'}$ represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group or a substituted aralkyl group;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Id):



(Id)

[in which R^6 represents a hydrogen atom or a hydroxyl group;

R^7 represents a hydrogen atom, a carboxyl group, a protected carboxyl group, or a group of formula $-B^3-T^4$ in which T^4 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group and B^3 represents an alkylene group which

has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ ;

R^9 represents a hydrogen atom or an alkylthio group having from 1 to 6 carbon atoms;

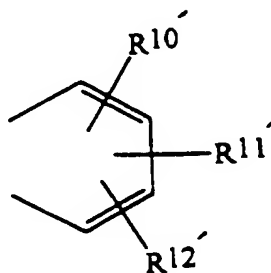
when R^9 represents an alkylthio group, R^7 and R^8 together represent a lactone group;

or

R^8 and R^9 together represent an oxo group];

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ie):



(Ie)

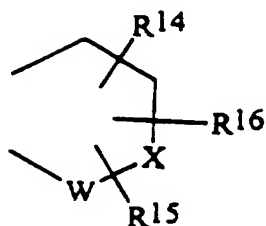
[in which $R^{10'}$ represents a hydroxyalkyl group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group, or a group of formula $-(O)_p-B^4-T^5$

in which T^5 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group, B^4 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or

is substituted by at least one of substituents γ , and, and p is as defined above];

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ic):



(Ic)

[in which R^{14} represents a hydroxyalkyl group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group or a group of formula $-(O)_p-B^4-T^5$ in which T^5 , B^4 and p are as defined above; R^{15} and R^{16} are the same or different, and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group; and Z is a methylene group, a group of formula $>NH$ or a group of formula $>N-$];

R^3 represents a hydrogen atom or an amino protecting group;

and

said substituents α are hydroxyl groups, aryl groups and aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

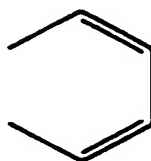
A further preferred class of compounds of the present invention are those compounds of formula (I) in which:

$R^{1'}$ represents a hydrogen atom;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (If):



(If)

R^3 represents a hydrogen atom, an aralkyl group, an aralkyl group which is substituted by at least one of substituents ϵ , defined below, or an aromatic acyl group;

Y^1 represents a hydrogen atom, an alkyl group having from 1 to 3 carbon atoms or a group of formula $-E'-COOH$;

Y^2 represents a hydrogen atom, an alkyl group having from 1 to 3 carbon atoms, an alkylthio group having from 1 to 3 carbon atoms or a group of formula $-E'-COOH$ or $-E'-Tet$, where Tet represents a tetrazolyl group;

Y^3 represents a group of formula $-E'-COOH$ or a group $-E'-Tet$, where Tet is as defined above;

Y^4 represents a hydrogen atom, an alkyl group having from 1 to 3 carbon atoms or a halogen atom; and

E' represents a direct bond, an alkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ , defined below, or an oxyalkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ , defined below;

and pharmaceutically acceptable salts and esters thereof.

Particularly preferred classes of compounds of the present invention are those compounds as defined above in which any one or any combination of two or more of the following restrictions also applies:

- (1) $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), as shown above.
- (2) R^3 represents an aralkyl group, an aralkyl group having one or more of substituents β or an aromatic acyl group.
- (3) R^3 represents an aralkyl group or an aralkyl group having one or more of substituents β .
- (4) R^3 represents a benzyl group or a benzyl group having one or more of substituents β .
- (5) Y^1 represents a hydrogen atom, a group of formula $-E'-COOH$, or a group of formula $-E'-Tet$, where E' and Tet are as defined above.
- (6) Y^1 represents a hydrogen atom.

(7) Y^2 represents a hydrogen atom, an alkylthio group having from 1 to 6, preferably from 1 to 3, carbon atoms, a group of formula $-E'-COOH$, or a group of formula $-E'-Tet$, where E' and Tet are as defined above.

(8) Y^2 represents an alkylthio group having from 1 to 6, preferably from 1 to 3, carbon atoms.

(9) Y^4 represents an alkyl group having from 1 to 6, preferably from 1 to 3, carbon atoms or a halogen atom.

(10) Y^4 represents an alkyl group having from 1 to 6, preferably from 1 to 3, carbon atoms.

(11) E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α , defined above, an oxyalkylene group having from 1 to 3 carbon atoms or a substituted oxyalkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α , defined above.

(12) E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α , defined above, or an oxyalkylene group having from 1 to 3 carbon atoms.

(13) E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α' , defined below, an oxyalkylene group having from 1 to 3 carbon atoms or a substituted oxyalkylene group which has from 1 to 3 carbon atoms and is substituted by at

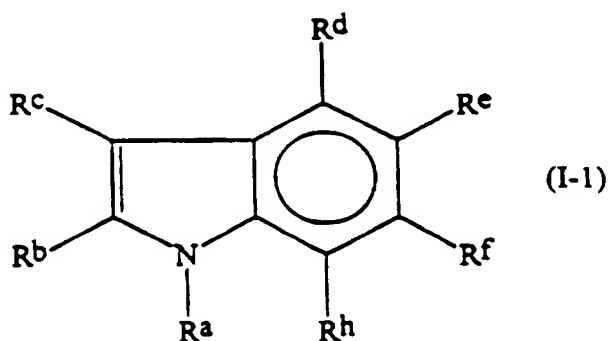
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least one of substituents α' , defined below.

(14) E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α' , defined below, or an oxyalkylene group having from 1 to 3 carbon atoms.

Substituents α' , referred to in (13) and (14) above are aralkyl groups and substituted aralkyl groups which are substituted by at least one of substituents β , defined above.

Examples of specific compounds of the present invention are the indole derivatives indicated by formula (I-1):



in which all substituent groups are as defined below, those not mentioned being hydrogen:

- 1-1. $R^a = CH_3$; $R^f = CH_2COOH$;
1-2. $R^a = Et$; $R^e = COOH$;
1-3. $R^a = Et$; $R^f = CH_2COOH$;
1-4. $R^a = Et$; $R^e = CH_2CH_2COOH$;
1-5. $R^a = iBu$; $R^e = CH_2COOH$;
1-6. $R^a = Bz$; $R^d = CH_2COOH$;
1-7. $R^a = Bz$; $R^d = CH_2COOH$; $R^h = CH_3$;
1-8. $R^a = Bz$; $R^d = CH_2COOH$; $R^h = SCH_3$;
1-9. $R^a = Bz$; $R^e = CH_2COOH$;
1-10. $R^a = Bz$; $R^f = CH_2COOH$;
1-11. $R^a = Bz$; $R^f = CH_2COOH$; $R^h = CH_3$;
1-12. $R^a = Bz$; $R^f = CH_2COOH$; $R^h = SCH_3$;
1-13. $R^a = Bz$; $R^h = CH_2COOH$;
1-14. $R^a = 2-ClBz$; $R^e = CH_2COOH$; $R^h = Et$;
1-15. $R^a = 4-ClBz$; $R^f = CH_2COOH$;
1-16. $R^a = Bz$; $R^f = CH_2COOH$; $R^h = Ph$;
1-17. $R^a = 3-FBz$; $R^f = CH_2COOH$;
1-18. $R^a = 4-FBz$; $R^f = CH_2COOH$; $R^h = SCH_3$;
1-19. $R^a = 3-MeOBz$; $R^e = CH_2COOH$;
1-20. $R^a = 4-MeOBz$; $R^e = CH_2COOH$; $R^h = SCH_3$;
1-21. $R^a = 3,4-diMeOBz$; $R^f = CH_2COOH$;
1-22. $R^a = Bz$; $R^f = CH(CH_3)COOH$;
1-23. $R^a = Bz$; $R^d = CH(Bz)COOH$; $R^h = SCH_3$;
1-24. $R^a = Bz$; $R^e = CH(Bz)COOH$;
1-25. $R^a = Bz$; $R^d = Cl$; $R^f = CH(Bz)COOH$;
1-26. $R^a = Bz$; $R^d = Cl$; $R^h = CH(Bz)COOH$;
1-27. $R^a = Bz$; $R^e = CH(3-ClBz)COOH$; $R^h = SCH_3$;
1-28. $R^a = Bz$; $R^d = CH_3$; $R^f = CH(4-FBz)COOH$;
1-29. $R^a = Bz$; $R^d = Ph$; $R^e = CH(3-MeOBz)COOH$;
1-30. $R^a = Bz$; $R^e = Cl$; $R^f = CH(3,4-diMeOBz)COOH$;
1-31. $R^a = 3-ClBz$; $R^e = CH(3-ClBz)COOH$;
1-32. $R^a = 3-ClBz$; $R^e = CH(3-FBz)COOH$; $R^h = SCH_3$;
1-33. $R^a = 3-ClBz$; $R^e = CH(3,4-diMeOBz)COOH$;
1-34. $R^a = 4-ClBz$; $R^f = CH(4-ClBz)COOH$; $R^h = SCH_3$;
1-35. $R^a = 3-FBz$; $R^e = CH(3-ClBz)COOH$;
1-36. $R^a = 3-FBz$; $R^f = CH(4-MeOBz)COOH$; $R^h = CH_3$;
1-37. $R^a = 4-FBz$; $R^f = CH(4-FBz)COOH$; $R^h = SCH_3$;

- 1-38. $R^a = 4\text{-FBz}$; $R^f = \text{CH}(4\text{-MeOBz})\text{COOH}$;
1-39. $R^a = 4\text{-MeOBz}$; $R^d = \text{CH}_3$; $R^e = \text{CH}(3\text{-ClBz})\text{COOH}$;
1-40. $R^a = 4\text{-MeOBz}$; $R^d = \text{F}$; $R^e = \text{CH}(3\text{-FBz})\text{COOH}$;
1-41. $R^a = 4\text{-MeOBz}$; $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$;
1-42. $R^a = 3\text{-ClBz}$; $R^d = \text{CH}_3$; $R^f = \text{CH}(\text{Bz})\text{COOH}$;
1-43. $R^a = 4\text{-ClBz}$; $R^f = \text{CH}(\text{Bz})\text{COOH}$;
1-44. $R^a = 2\text{-FBz}$; $R^d = \text{CH}_3$; $R^e = \text{CH}(\text{Bz})\text{COOH}$;
1-45. $R^a = 2\text{-FBz}$; $R^e = \text{CH}(\text{Bz})\text{COOH}$;
1-46. $R^a = 3\text{-FBz}$; $R^f = \text{CH}(\text{Bz})\text{COOH}$;
1-47. $R^a = 3\text{-FBz}$; $R^d = \text{CH}_3$; $R^f = \text{CH}(\text{Bz})\text{COOH}$;
1-48. $R^a = 4\text{-FBz}$; $R^e = \text{CH}(\text{Bz})\text{COOH}$;
1-49. $R^a = 4\text{-MeOBz}$; $R^f = \text{CH}(\text{Bz})\text{COOH}$;
1-50. $R^a = 4\text{-MeOBz}$; $R^f = \text{CH}(\text{Bz})\text{COOH}$; $R^h = \text{SCH}_3$;
1-51. $R^a = 3,4\text{-diMeOBz}$; $R^e = \text{CH}(\text{Bz})\text{COOH}$;
1-52. $R^a = 3,4\text{-diMeOBz}$; $R^d = \text{CH}_3$; $R^e = \text{CH}(\text{Bz})\text{COOH}$;
1-53. $R^a = 3,4\text{-diMeOBz}$; $R^f = \text{CH}(\text{Bz})\text{COOH}$;
1-54. $R^a = 3,4\text{-diMeOBz}$; $R^d = \text{CH}_3$; $R^f = \text{CH}(\text{Bz})\text{COOH}$;
 $R^h = \text{SCH}_3$;
1-55. $R^a = 4\text{-NH}_2\text{Bz}$; $R^f = \text{CH}(\text{Bz})\text{COOH}$; $R^h = \text{SCH}_3$;
1-56. $R^a = \text{Bz}$; $R^f = \text{CH}(2\text{-PhEt})\text{COOH}$; $R^h = \text{SCH}_3$;
1-57. $R^a = \text{Bz}$; $R^f = \text{CH}_2\text{CH}_2\text{COOH}$;
1-58. $R^a = 2\text{-ClBz}$; $R^e = \text{CH}_2\text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
1-59. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{CH}_2\text{COOH}$;
1-60. $R^a = 4\text{-ClBz}$; $R^f = \text{CH}_2\text{CH}_2\text{COOH}$; $R^e = \text{CH}_3$;
1-61. $R^a = 2\text{-FBz}$; $R^f = \text{CH}_2\text{CH}_2\text{COOH}$;
1-62. $R^a = 4\text{-FBz}$; $R^e = \text{CH}_2\text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
1-63. $R^a = 2\text{-MeOBz}$; $R^e = \text{CH}_2\text{CH}_2\text{COOH}$;
1-64. $R^a = 4\text{-MeOBz}$; $R^d = \text{CH}_3$; $R^f = \text{CH}_2\text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
1-65. $R^a = 3,4\text{-diMeOBz}$; $R^e = \text{CH}_2\text{CH}_2\text{COOH}$; $R^h = \text{Pr}$;
1-66. $R^a = 4\text{-NH}_2\text{Bz}$; $R^e = \text{CH}_2\text{CH}_2\text{COOH}$;
1-67. $R^a = \text{Bz}$; $R^e = \text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$;
1-68. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^e = \text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
1-69. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^d = \text{CH}_3$; $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$;
1-70. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^f = \text{CH}(2\text{-PhEt})\text{COOH}$;
1-71. $R^a = \text{Bz}$; $R^b = \text{Ph}$; $R^e = \text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
1-72. $R^a = \text{Bz}$; $R^b = \text{Ph}$; $R^d = \text{CH}_3$; $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$;
1-73. $R^a = \text{Bz}$; $R^b = \text{Ph}$; $R^f = \text{CH}(2\text{-PhEt})\text{COOH}$;

- 1-74. $R^a = \text{Bz}$; $R^c = \text{Ph}$; $R^e = \text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
- 1-75. $R^a = \text{Bz}$; $R^c = \text{Ph}$; $R^d = \text{CH}_3$; $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$;
- 1-76. $R^a = \text{Bz}$; $R^c = \text{Ph}$; $R^f = \text{CH}(2\text{-PhEt})\text{COOH}$;
- 1-77. $R^a = 4\text{-FBz}$; $R^c = \text{Bz}$; $R^f = \text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
- 1-78. $R^a = 3\text{-MeOBz}$; $R^c = \text{Bz}$; $R^d = \text{CH}_3$; $R^e = \text{CH}_2\text{COOH}$;
- 1-79. $R^a = 4\text{-ClBz}$; $R^c = \text{Bz}$; $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$;
 $R^h = \text{CH}_3$;
- 1-80. $R^a = 4\text{-FBz}$; $R^b = \text{CH}_3$; $R^c = \text{Ph}$; $R^f = \text{CH}_2\text{COOH}$;
- 1-81. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^c = \text{Ph}$; $R^e = \text{CH}(\text{Bz})\text{COOH}$;
 $R^h = \text{SCH}_3$;
- 1-82. $R^a = 3\text{-ClBz}$; $R^b = \text{CH}_3$; $R^c = \text{Ph}$; $R^e = \text{CH}(3\text{-FBz})\text{COOH}$;
- 1-83. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^c = \text{Ph}$; $R^e = \text{CH}(2\text{-PhEt})\text{COOH}$;
 $R^h = \text{CH}_3$;
- 1-84. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^c = \text{Ph}$; $R^f = \text{CH}_2\text{CH}_2\text{COOH}$;
- 1-85. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^c = \text{Bz}$; $R^e = \text{CH}_2\text{COOH}$;
 $R^h = \text{SCH}_3$;
- 1-86. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^c = \text{Bz}$; $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$;
- 1-87. $R^a = 3\text{-FBz}$; $R^b = \text{CH}_3$; $R^c = \text{Bz}$;
 $R^e = \text{CH}(3\text{-ClBz})\text{COOH}$;
- 1-88. $R^a = 4\text{-NH}_2\text{Bz}$; $R^b = \text{CH}_3$; $R^c = \text{Bz}$; $R^d = \text{CH}_3$;
 $R^f = \text{CH}(\text{Bz})\text{COOH}$;
- 1-89. $R^a = 4\text{-FBz}$; $R^b = \text{CH}_3$; $R^c = 2\text{-PhEt}$; $R^d = \text{CH}_3$;
 $R^f = \text{CH}_2\text{COOH}$;
- 1-90. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^c = 2\text{-PhEt}$;
 $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$; $R^h = \text{SCH}_3$;
- 1-91. $R^a = 4\text{-FBz}$; $R^b = \text{CH}_3$; $R^c = 2\text{-PhEt}$;
 $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$;
- 1-92. $R^a = 4\text{-ClBz}$; $R^b = \text{CH}_3$; $R^c = 2\text{-PhEt}$;
 $R^f = \text{CH}(\text{Bz})\text{COOH}$;
- 1-93. $R^a = 4\text{-ClBz}$; $R^b = \text{Ph}$; $R^c = 2\text{-PhEt}$; $R^f = \text{CH}_2\text{COOH}$;
- 1-94. $R^a = 3\text{-ClBz}$; $R^b = \text{Ph}$; $R^c = 2\text{-PhEt}$;
 $R^e = \text{CH}(3\text{-FBz})\text{COOH}$;
- 1-95. $R^a = 3,4\text{-diMeOBz}$; $R^b = \text{Ph}$; $R^c = 2\text{-PhEt}$;
 $R^f = \text{CH}(\text{Bz})\text{COOH}$; $R^h = \text{CH}_3$;
- 1-96. $R^a = 4\text{-ClBz}$; $R^b = \text{Ph}$; $R^c = \text{Pr}$; $R^f = \text{CH}_2\text{COOH}$;
 $R^h = \text{CH}_3$;
- 1-97. $R^a = \text{Bz}$; $R^b = \text{Ph}$; $R^c = \text{Pr}$; $R^e = \text{CH}(\text{Bz})\text{COOH}$;
 $R^h = \text{SCH}_3$;

- 1-98. $R^a = 3\text{-ClBz}$; $R^b = \text{Ph}$; $R^c = \text{Pr}$; $R^e = \text{CH}(3\text{-FBz})\text{COOH}$;
- 1-99. $R^a = 4\text{-ClBz}$; $R^b = \text{Et}$; $R^c = \text{Pr}$; $R^d = \text{SCH}_3$;
 $R^f = \text{CH}_2\text{COOH}$;
- 1-100. $R^a = \text{Bz}$; $R^b = \text{Et}$; $R^c = \text{Pr}$; $R^e = \text{CH}(\text{Bz})\text{COOH}$;
 $R^h = \text{Ph}$
- 1-101. $R^a = 3\text{-ClBz}$; $R^b = \text{Et}$; $R^c = \text{Pr}$;
 $R^e = \text{CH}(3\text{-FBz})\text{COOH}$; $R^h = \text{SCH}_3$;
- 1-102. $R^a = 4\text{-FBz}$; $R^b = \text{Bz}$; $R^c = 2\text{-PhEt}$; $R^f = \text{CH}_2\text{COOH}$;
 $R^h = \text{Et}$;
- 1-103. $R^a = \text{Bz}$; $R^b = \text{Bz}$; $R^c = 2\text{-PhEt}$;
 $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$;
- 1-104. $R^a = 3\text{-FBz}$; $R^b = \text{Bz}$; $R^c = 2\text{-PhEt}$;
 $R^e = \text{CH}(3\text{-ClBz})\text{COOH}$;
- 1-105. $R^a = \text{Bz}$; $R^b = 4\text{-FBz}$; $R^c = 2\text{-PhEt}$; $R^e = \text{CH}_2\text{COOH}$;
- 1-106. $R^a = \text{Bz}$; $R^b = \text{Bz}$; $R^c = 2\text{-PhEt}$;
 $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$; $R^h = \text{CH}_3$;
- 1-107. $R^a = 3\text{-FBz}$; $R^b = \text{Bz}$; $R^c = 3\text{-FPhEt}$;
 $R^e = \text{CH}(3\text{-ClBz})\text{COOH}$;
- 1-108. $R^a = \text{Bz}$; $R^b = 4\text{-FBz}$; $R^c = \text{Bz}$; $R^e = \text{CH}_2\text{COOH}$;
 $R^h = \text{SCH}_3$;
- 1-109. $R^a = \text{Bz}$; $R^b = \text{Bz}$; $R^c = \text{Bz}$; $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$;
- 1-110. $R^a = 3\text{-ClBz}$; $R^b = 3\text{-MeOBz}$; $R^c = \text{Bz}$;
 $R^e = \text{CH}(3\text{-FBz})\text{COOH}$;
- 1-111. $R^a = 4\text{-FBz}$; $R^f = \text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
- 1-112. $R^a = \text{Bz}$; $R^d = \text{CH}_3$; $R^f = \text{CH}(4\text{-FBz})\text{COOH}$;
- 1-113. $R^a = 3\text{-ClBz}$; $R^e = \text{CH}(3\text{-FBz})\text{COOH}$;
- 1-114. $R^a = 4\text{-MeOBz}$; $R^e = \text{CH}(3\text{-ClBz})\text{COOH}$;
- 1-115. $R^a = \text{Bz}$; $R^f = \text{CH}(2\text{-PhEt})\text{COOH}$; $R^h = \text{CH}_3$;
- 1-116. $R^a = 4\text{-ClBz}$; $R^f = \text{CH}_2\text{CH}_2\text{COOH}$; $R^h = \text{F}$;
- 1-117. $R^a = 4\text{-FBz}$; $R^f = \text{CH}_2\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$; $R^h = \text{SCH}_3$;
- 1-118. $R^a = \text{Bz}$; $R^f = \text{CH}(4\text{-FBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
- 1-119. $R^a = 3\text{-ClBz}$; $R^d = \text{CH}_3$;
 $R^e = \text{CH}(3\text{-FBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
- 1-120. $R^a = 4\text{-MeOBz}$; $R^e = \text{CH}(3\text{-ClBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
- 1-121. $R^a = \text{Bz}$; $R^f = \text{CH}(2\text{-PhEt})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
 $R^h = \text{SCH}_3$;
- 1-122. $R^a = 4\text{-ClBz}$; $R^f = \text{CH}_2\text{CH}_2\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;

- 1-123. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{COOCH}_3$; $R^h = \text{SCH}_3$;
1-124. $R^a = \text{Bz}$; $R^f = \text{CH}(4\text{-FBz})\text{COOCH}_3$;
1-125. $R^a = 3\text{-FBz}$; $R^d = \text{CH}_3$; $R^f = \text{CH}(4\text{-FBz})\text{COOCH}_3$;
1-126. $R^a = \text{Bz}$; $R^f = \text{CH}(2\text{-PhEt})\text{COOCH}_3$;
1-127. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{COOEt}$;
1-128. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{COOEt}$; $R^h = \text{SCH}_3$;
1-129. $R^a = 3\text{-ClBz}$; $R^e = \text{CH}(3\text{-FBz})\text{COOEt}$;
1-130. $R^a = 3\text{-FBz}$; $R^f = \text{CH}(4\text{-FBz})\text{COOEt}$;
1-131. $R^a = \text{Bz}$; $R^d = \text{CH}_3$; $R^f = \text{CH}(2\text{-PhEt})\text{COOEt}$;
1-132. $R^a = \text{Bz}$; $R^f = \text{CH}(2\text{-PhEt})\text{COOEt}$;
1-133. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{OCOCH}_3$;
1-134. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{OCOCH}_3$; $R^h = \text{SCH}_3$;
1-135. $R^a = 3\text{-ClBz}$; $R^e = \text{CH}(3\text{-FBz})\text{COOCH}_2\text{CH}_2\text{OCOCH}_3$;
1-136. $R^a = 4\text{-MeOBz}$; $R^e = \text{CH}(3\text{-ClBz})\text{COOCH}_2\text{CH}_2\text{OCOCH}_3$;
 $R^h = \text{CH}_3$;
1-137. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
1-138. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $R^h = \text{SCH}_3$;
1-139. $R^a = 3\text{-ClBz}$; $R^e = \text{CH}(3\text{-FBz})\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
1-140. $R^a = 4\text{-MeOBz}$; $R^e = \text{CH}(3\text{-ClBz})\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
1-141. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{CONHCH}_3$;
1-142. $R^a = \text{Bz}$; $R^f = \text{CH}(4\text{-FBz})\text{CONHCH}_3$;
1-143. $R^a = \text{Bz}$; $R^f = \text{CH}(4\text{-FBz})\text{CONHCH}_3$; $R^h = \text{SCH}_3$;
1-144. $R^a = 3\text{-FBz}$; $R^f = \text{CH}(4\text{-FBz})\text{CONHCH}_3$;
1-145. $R^a = \text{Bz}$; $R^f = \text{CH}(2\text{-PhEt})\text{CONHCH}_3$;
1-146. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{CONHCH}_2\text{CH}_2\text{OH}$;
1-147. $R^a = \text{Bz}$; $R^f = \text{CH}(4\text{-FBz})\text{CONHCH}_2\text{CH}_2\text{OH}$;
1-148. $R^a = \text{Bz}$; $R^f = \text{CH}(4\text{-FBz})\text{CONHCH}_2\text{CH}_2\text{OH}$; $R^h = \text{CH}_3$;
1-149. $R^a = 4\text{-MeOBz}$; $R^e = \text{CH}(3\text{-ClBz})\text{CONHCH}_2\text{CH}_2\text{OH}$;
1-150. $R^a = 4\text{-ClBz}$; $R^f = \text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{OH}$;
1-151. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
1-152. $R^a = 3\text{-ClBz}$; $R^f = \text{CH}_2\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $R^h = \text{CH}_3$;
1-153. $R^a = \text{Bz}$; $R^f = \text{CH}(4\text{-FBz})\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
1-154. $R^a = 4\text{-MeOBz}$; $R^e = \text{CH}(3\text{-ClBz})\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
1-155. $R^a = 4\text{-ClBz}$; $R^f = \text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
1-156. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^f = \text{OCH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
1-157. $R^a = 3\text{-FBz}$; $R^b = \text{CH}_3$; $R^d = \text{CH}_3$; $R^f = \text{OCH}_2\text{COOH}$;
1-158. $R^a = 3,4\text{-diMeOBz}$; $R^b = \text{CH}_3$; $R^f = \text{OCH}_2\text{COOH}$;

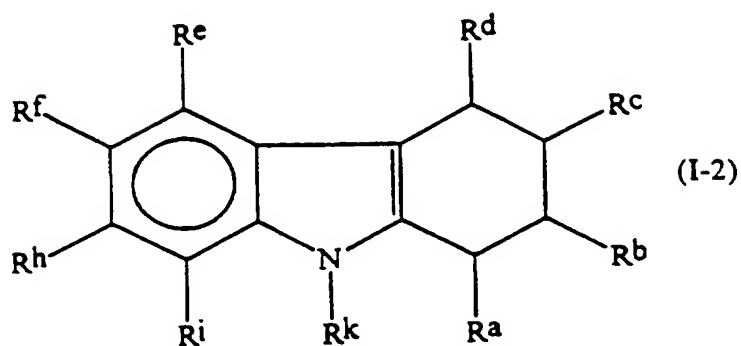
- 1-159. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^f = \text{OCH}(4\text{-FBz})\text{COOH}$; $R^h = \text{SCH}_3$;
 1-160. $R^a = 3\text{-ClBz}$; $R^b = \text{CH}_3$; $R^e = \text{OCH}(3,4\text{-diMeOBz})\text{COOH}$;
 1-161. $R^a = 4\text{-MeOBz}$; $R^b = \text{CH}_3$; $R^e = \text{OCH}(3\text{-ClBz})\text{COOH}$;
 1-162. $R^a = 2\text{-FBz}$; $R^b = \text{CH}_3$; $R^e = \text{OCH}(\text{Bz})\text{COOH}$; $R^h = \text{CH}_3$;
 1-163. $R^a = 2\text{-FBz}$; $R^b = \text{CH}_3$;
 $R^e = \text{OCH}(\text{Bz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$; $R^h = \text{CH}_3$;
 1-164. $R^a = \text{Bz}$; $R^b = \text{CH}_3$;
 $R^f = \text{OCH}(4\text{-FBz})\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $R^h = \text{SCH}_3$;
 1-165. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^f = \text{OCH}_2\text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
 1-166. $R^a = 3\text{-FBz}$; $R^b = \text{CH}_3$; $R^d = \text{CH}_3$; $R^f = \text{OCH}_2\text{CH}_2\text{COOH}$;
 1-167. $R^a = 3,4\text{-diMeOBz}$; $R^b = \text{CH}_3$; $R^f = \text{OCH}_2\text{CH}_2\text{COOH}$;
 1-168. $R^a = \text{Bz}$; $R^b = \text{CH}_3$; $R^f = \text{OCH}_2\text{CH}(4\text{-FBz})\text{COOH}$;
 $R^h = \text{SCH}_3$;
 1-169. $R^a = 3\text{-ClBz}$; $R^b = \text{CH}_3$;
 $R^e = \text{OCH}_2\text{CH}(3,4\text{-diMeOBz})\text{COOH}$;
 1-170. $R^a = 4\text{-MeOBz}$; $R^b = \text{CH}_3$; $R^e = \text{OCH}_2\text{CH}(3\text{-ClBz})\text{COOH}$;
 1-171. $R^a = 2\text{-FBz}$; $R^b = \text{CH}_3$;
 $R^e = \text{OCH}_2\text{CH}(\text{Bz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$; $R^h = \text{CH}_3$;
 1-172. $R^a = 2\text{-FBz}$; $R^b = \text{CH}_3$;
 $R^e = \text{OCH}_2\text{CH}(\text{Bz})\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $R^h = \text{SCH}_3$;
 1-173. $R^a = \text{COPh}$; $R^f = \text{CH}(\text{Bz})\text{COOH}$; $R^h = \text{SCH}_3$;
 1-174. $R^a = \text{COPh}$; $R^f = \text{CH}_2\text{COOH}$;
 1-175. $R^a = \text{CO}(2\text{-Cl-Ph})$; $R^e = \text{CH}(3\text{-MeOBz})\text{COOH}$; $R^h = \text{SCH}_3$;
 1-176. $R^a = \text{CO}(3\text{-Cl-Ph})$; $R^f = \text{CH}_2\text{COOH}$;
 1-177. $R^a = \text{CO}(4\text{-Cl-Ph})$; $R^f = \text{CH}_2\text{COOH}$; $R^e = \text{CH}_3$;
 1-178. $R^a = \text{CO}(2\text{-F-Ph})$; $R^f = \text{CH}(3\text{-F-Ph})\text{COOH}$;
 1-179. $R^a = \text{CO}(4\text{-F-Ph})$; $R^e = \text{CH}_2\text{COOH}$; $R^h = \text{SCH}_3$;
 1-180. $R^a = \text{CO}(2\text{-MeO-Ph})$; $R^e = \text{CH}(4\text{-FBz})\text{COOH}$;
 1-181. $R^a = \text{CO}(4\text{-MeO-Ph})$; $R^d = \text{CH}_3$; $R^f = \text{CH}_2\text{COOH}$;
 $R^h = \text{SCH}_3$;
 1-182. $R^a = \text{CO}(3,4\text{-MeO-Ph})$; $R^e = \text{CH}(3\text{-ClBz})\text{COOH}$; $R^h = \text{Pr}$;
 1-183. $R^a = \text{CO}(4\text{-NH}_2\text{-Ph})$; $R^e = \text{CH}_2\text{COOH}$;
 1-184. $R^a = \text{CO}(4\text{-F-Ph})$; $R^e = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
 $R^h = \text{SCH}_3$;
 1-185. $R^a = \text{CO}(4\text{-F-Ph})$; $R^e = \text{CH}(\text{Bz})\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
 $R^h = \text{SCH}_3$;
 1-186. $R^a = \text{CO}(2\text{-MeO-Ph})$; $R^e = \text{CH}(\text{Bz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;

- 1-187. $R^a = \text{COCH}_3$; $R^f = \text{CH}(\text{Bz})\text{COOH}$; $R^h = \text{SCH}_3$;
 1-188. $R^a = \text{COCH}_3$; $R^f = \text{CH}_2\text{COOH}$;
 1-189. $R^a = \text{COCH}(\text{CH}_3)_2$; $R^e = \text{CH}_2\text{COOH}$;
 1-190. $R^a = \text{COCH}(\text{CH}_3)_2$; $R^f = \text{CH}(\text{Bz})\text{COOH}$; $R^h = \text{SCH}_3$;
 1-191. $R^a = \text{COCH}(\text{CH}_3)_2$; $R^e = \text{CH}(\text{Bz})\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
 $R^h = \text{SCH}_3$;
 1-192. $R^a = \text{COCH}(\text{CH}_3)_2$; $R^e = \text{CH}(\text{Bz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
 1-193. $R^a = \text{COCHEt}$; $R^e = \text{CH}_2\text{COOH}$;
 1-194. $R^a = \text{COCHEt}$; $R^e = \text{CH}(\text{Bz})\text{COOH}$;
 1-195. $R^a = \text{COCHCH}_2(\text{CH}_3)_2$; $R^e = \text{CH}_2\text{COOH}$;
 1-196. $R^a = \text{COCHCH}_2(\text{CH}_3)_2$; $R^f = \text{CH}(\text{Bz})\text{COOH}$; $R^h = \text{SCH}_3$;
 1-197. $R^a = \text{COCHCH}_2(\text{CH}_3)_2$; $R^e = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
 $R^h = \text{SCH}_3$;
 1-198. $R^a = \text{COCHCH}_2(\text{CH}_3)_2$; $R^e = \text{CH}(\text{Bz})\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;
 $R^h = \text{SCH}_3$;
 1-199. $R^a = \text{COCHCH}_2(\text{CH}_3)_2$; $R^e = \text{CH}(\text{Bz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
 1-200. $R^a = \text{COCHCH}_2(\text{CH}_3)_2$; $R^e = \text{CH}(\text{Bz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
 $R^h = \text{SCH}_3$;
 1-201. $R^a = \text{Bz}$; $R^e = \text{CH}_2\text{Tet}$;
 1-202. $R^a = \text{Bz}$; $R^f = \text{CH}_2\text{Tet}$;
 1-203. $R^a = \text{Bz}$; $R^f = \text{CH}_2\text{CH}_2\text{Tet}$;
 1-204. $R^a = 4\text{-FBz}$; $R^f = \text{CH}_2\text{CH}_2\text{CH}_2\text{Tet}$;
 1-205. $R^a = \text{Bz}$; $R^e = \text{CH}_2\text{CH}_2\text{Tet}$;
 1-206. $R^a = \text{Bz}$; $R^d = \text{Tet}$;
 1-207. $R^a = (3\text{-MeO})\text{PhCH}_2$; $R^h = \text{Tet}$;
 1-208. $R^a = \text{Bz}$; $R^d = \text{CH}_2\text{Tet}$;
 1-209. $R^a = \text{Bz}$; $R^h = \text{CH}_2\text{Tet}$;
 1-210. $R^a = (4\text{-F})\text{PhCH}_2$; $R^d = \text{SO}_2\text{NHCOCH}_3$;
 1-211. $R^a = \text{Bz}$; $R^e = \text{SO}_2\text{NHCOCH}_3$;
 1-212. $R^a = \text{Bz}$; $R^f = \text{SO}_2\text{NHCOCH}_3$;
 1-213. $R^a = (4\text{-NO}_2)\text{PhCH}_2$; $R^h = \text{SO}_2\text{NHCOCH}_3$;
 1-214. $R^a = \text{Bz}$; $R^d = \text{SO}_2\text{NHCOCH}_2\text{CH}_3$;
 1-215. $R^a = \text{Bz}$; $R^e = \text{SO}_2\text{NHCOCH}_2\text{CH}_3$;
 1-216. $R^a = \text{Bz}$; $R^f = \text{SO}_2\text{NHCOCH}_2\text{CH}_3$;
 1-217. $R^a = \text{Bz}$; $R^h = \text{SO}_2\text{NHCOCH}_2\text{CH}_3$;
 1-218. $R^a = \text{Bz}$; $R^d = \text{SO}_2\text{NHCOCH}_2\text{Ph}$;
 1-219. $R^a = (4\text{-Cl})\text{PhCH}_2$; $R^e = \text{SO}_2\text{NHCOCH}_2\text{Ph}$;

- 1-220. $R^a = \text{Bz}$; $R^f = \text{SO}_2\text{NHCOCH}_2\text{Ph}$;
1-221. $R^a = \text{Bz}$; $R^h = \text{SO}_2\text{NHCOCH}_2\text{Ph}$;
1-222. $R^a = \text{Bz}$; $R^d = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$;
1-223. $R^a = \text{Bz}$; $R^e = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$;
1-224. $R^a = 4-(\text{CF}_3)\text{PhCH}_2$; $R^f = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$;
1-225. $R^a = \text{Bz}$; $R^h = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$;
1-226. $R^a = \text{Bz}$; $R^d = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{CH}_3$;
1-227. $R^a = \text{Bz}$; $R^e = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{CH}_3$;
1-228. $R^a = \text{Bz}$; $R^f = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{CH}_3$;
1-229. $R^a = (4\text{-MeO})\text{PhCH}_2$; $R^h = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{CH}_3$;
1-230. $R^a = \text{Bz}$; $R^d = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{Ph}$;
1-231. $R^a = \text{Bz}$; $R^e = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{Ph}$;
1-232. $R^a = \text{Bz}$; $R^f = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{Ph}$;
1-233. $R^a = \text{Bz}$; $R^h = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{Ph}$;
1-234. $R^a = \text{Bz}$; $R^d = \text{Tet}$;
1-235. $R^a = 4-(\text{MeO}_2\text{C})\text{Bz}$;
1-236. $R^a = 4-(\text{HOOC})\text{Bz}$;
1-237. $R^a = 4\text{-Tet-Bz}$;
1-238. $R^a = 4\text{-Ph-Bz}$; $R^d = \text{CN}$;
1-239. $R^a = 4\text{-Ph-Bz}$; $R^d = \text{CH}_2\text{COOH}$;
1-240. $R^a = \text{Bz}$; $R^b = \text{Me}$; $R^c = \text{Me}$; $R^f = \text{CH}_2\text{COOH}$;
1-241. $R^a = \text{Bz}$; $R^b = \text{Me}$; $R^c = \text{Me}$; $R^f = \text{CH}_2\text{Tet}$.

Of these, the preferred compounds are Nos. 1-12, 1-23, 1-33, 1-34, 1-37, 1-51, 1-54, 1-68, 1-71, 1-74, 1-77, 1-81, 1-93, 1-99, 1-111, 1-117, 1-123, 1-134, 1-138, 1-148, 1-159, 1-168, 1-173, 1-197, 1-202, 1-208, 1-212, 1-219, 1-223, 1-239 and 1-241 and the most preferred are Nos. 1-12, 1-34, 1-37, 1-77, 1-93, 1-202, 1-208, 1-219 and 1-239.

Further examples of specific compounds of the present invention are the tetrahydrocarbazole derivatives indicated by formula (I-2):



in which all substituent groups are as defined below,
those not mentioned being hydrogen:

- 2-1. $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{CH}_3$;
- 2-2. $R^c = \text{COOH}$; $R^k = \text{Et}$;
- 2-3. $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{Et}$;
- 2-4. $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = \text{Et}$;
- 2-5. $R^c = \text{CH}_2\text{COOH}$; $R^k = i\text{Bu}$;
- 2-6. $R^a = \text{CH}_2\text{COOH}$; $R^k = \text{Bz}$;
- 2-7. $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{Bz}$;
- 2-8. $R^c = \text{CH}_2\text{COOH}$; $R^k = \text{Bz}$;
- 2-9. $R^d = \text{CH}_2\text{COOH}$; $R^k = \text{Bz}$;
- 2-10. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{Bz}$;
- 2-11. $R^c = \text{CH}_2\text{COOH}$; $R^k = \text{Bz}$;
- 2-12. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{Bz}$;
- 2-13. $R^a = \text{SCH}_3$; $R^c = \text{CH}_2\text{COOH}$; $R^k = \text{Bz}$;
- 2-14. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{SCH}_3$; $R^k = \text{Bz}$;
- 2-15. $R^a = \text{Et}$; $R^c = \text{CH}_2\text{COOH}$; $R^k = 2\text{-ClBz}$;
- 2-16. $R^b = \text{CH}_2\text{COOH}$; $R^k = 4\text{-ClBz}$;
- 2-17. $R^a = \text{Ph}$; $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{Bz}$;
- 2-18. $R^b = \text{CH}_2\text{COOH}$; $R^k = 3\text{-FBz}$;

- 2-19. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^k = 4\text{-FBz}$;
2-20. $R^c = \text{CH}_2\text{COOH}$; $R^k = 3\text{-MeOBz}$;
2-21. $R^a = \text{SCH}_3$; $R^c = \text{CH}_2\text{COOH}$; $R^k = 4\text{-MeOBz}$;
2-22. $R^b = \text{CH}_2\text{COOH}$; $R^k = 3,4\text{-diMeOBz}$;
2-23. $R^b = \text{CH}(\text{CH}_3)\text{COOH}$; $R^k = \text{Bz}$;
2-24. $R^a = \text{SCH}_3$; $R^d = \text{CH}(\text{Bz})\text{COOH}$; $R^k = \text{Bz}$;
2-25. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^k = \text{Bz}$;
2-26. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^e = \text{Cl}$ $R^k = \text{Bz}$;
2-27. $R^a = \text{CH}(\text{Bz})\text{COOH}$; $R^h = \text{Cl}$ $R^k = \text{Bz}$;
2-28. $R^a = \text{SCH}_3$; $R^c = \text{CH}(3\text{-ClBz})\text{COOH}$; $R^k = \text{Bz}$;
2-29. $R^b = \text{CH}(4\text{-FBz})\text{COOH}$; $R^d = \text{CH}_3$; $R^e = \text{OH}$; $R^k = \text{Bz}$;
2-30. $R^c = \text{CH}(3\text{-MeOBz})\text{COOH}$; $R^d = \text{Ph}$; $R^e = \text{OCH}_3$; $R^k = \text{Bz}$;
2-31. $R^b = \text{CH}(3,4\text{-diMeOBz})\text{COOH}$; $R^e = \text{Cl}$; $R^k = \text{Bz}$;
2-32. $R^c = \text{CH}(3\text{-ClBz})\text{COOH}$; $R^f = \text{F}$ $R^k = 3\text{-ClBz}$;
2-33. $R^a = \text{SCH}_3$; $R^c = \text{CH}(3\text{-FBz})\text{COOH}$; $R^k = 3\text{-ClBz}$;
2-34. $R^c = \text{CH}(3,4\text{-diMeOBz})\text{COOH}$; $R^k = 3\text{-ClBz}$;
2-35. $R^a = \text{SCH}_3$; $R^b = \text{CH}(4\text{-ClBz})\text{COOH}$; $R^k = 4\text{-ClBz}$;
2-36. $R^c = \text{CH}(3\text{-ClBz})\text{COOH}$; $R^k = 3\text{-FBz}$;
2-37. $R^a = \text{CH}_3$; $R^b = \text{CH}(4\text{-MeOBz})\text{COOH}$; $R^k = 3\text{-FBz}$;
2-38. $R^a = \text{SCH}_3$; $R^b = \text{CH}(4\text{-FBz})\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = 4\text{-FBz}$;
2-39. $R^b = \text{CH}(4\text{-MeOBz})\text{COOH}$; $R^k = 4\text{-FBz}$;
2-40. $R^c = \text{CH}(3\text{-ClBz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 4\text{-MeOBz}$;
2-41. $R^c = \text{CH}(3\text{-FBz})\text{COOH}$; $R^e = \text{OH}$; $R^k = 4\text{-MeOBz}$;
2-42. $R^c = \text{CH}(3\text{-MeOBz})\text{COOH}$; $R^f = \text{OH}$; $R^k = 4\text{-MeOBz}$;
2-43. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 3\text{-ClBz}$;
2-44. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 4\text{-ClBz}$;
2-45. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 2\text{-FBz}$;
2-46. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 2\text{-FBz}$;
2-47. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^f = \text{Cl}$; $R^k = 3\text{-FBz}$;
2-48. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 3\text{-FBz}$;
2-49. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 4\text{-FBz}$;
2-50. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^e = \text{F}$; $R^k = 4\text{-MeOBz}$;
2-51. $R^a = \text{SCH}_3$; $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 4\text{-MeOBz}$;
2-52. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 3,4\text{-diMeOBz}$;
2-53. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 3,4\text{-diMeOBz}$;
2-54. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 3,4\text{-diMeOBz}$;

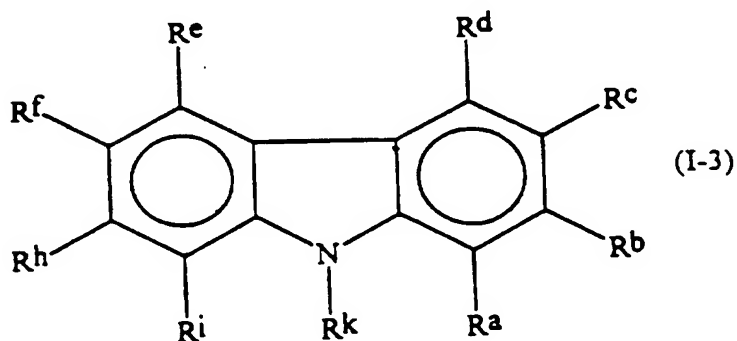
- 2-55. $R^a = \text{SCH}_3$; $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = 3,4\text{-diMeOBz}$;
- 2-56. $R^a = \text{SCH}_3$; $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 4\text{-NH}_2\text{Bz}$;
- 2-57. $R^a = \text{SCH}_3$; $R^b = \text{CH}(2\text{-PhEt})\text{COOH}$; $R^k = \text{Bz}$;
- 2-58. $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^f = \text{OH}$; $R^k = \text{Bz}$;
- 2-59. $R^a = \text{SCH}_3$; $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 2\text{-ClBz}$;
- 2-60. $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 3\text{-ClBz}$;
- 2-61. $R^c = \text{CH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^f = \text{F}$; $R^k = 4\text{-ClBz}$;
- 2-62. $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 2\text{-FBz}$;
- 2-63. $R^a = \text{SCH}_3$; $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 4\text{-FBz}$;
- 2-64. $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 2\text{-MeOBz}$;
- 2-65. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = 4\text{-MeOBz}$;
- 2-66. $R^a = \text{Pr}$; $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 3,4\text{-diMeOBz}$;
- 2-67. $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^e = \text{OCH}_3$; $R^k = 4\text{-NH}_2\text{Bz}$;
- 2-68. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^e = \text{CH}_3$; $R^k = \text{Bz}$;
- 2-69. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^f = \text{CH}_3$; $R^k = 3\text{-FBz}$;
- 2-70. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^k = 3,4\text{-diMeOBz}$;
- 2-71. $R^a = \text{SCH}_3$; $R^b = \text{CH}(4\text{-FBz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{Bz}$;
- 2-72. $R^c = \text{CH}(3,4\text{-diMeOBz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 3\text{-ClBz}$;
- 2-73. $R^c = \text{CH}(3\text{-ClBz})\text{COOH}$; $R^e = \text{OH}$; $R^k = 4\text{-MeOBz}$;
- 2-74. $R^a = \text{CH}_3$; $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^f = \text{F}$; $R^k = 2\text{-FBz}$;
- 2-75. $R^a = \text{SCH}_3$; $R^c = \text{CH}_2\text{COOH}$; $R^f = \text{Ph}$; $R^k = \text{Bz}$;
- 2-76. $R^a = \text{CH}_3$; $R^c = \text{CH}(3\text{-MeOBz})\text{COOH}$; $R^k = \text{Bz}$;
- 2-77. $R^b = \text{CH}(2\text{-PhEt})\text{COOH}$; $R^d = \text{Ph}$; $R^k = \text{Bz}$;
- 2-78. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^f = \text{Bz}$; $R^k = 4\text{-FBz}$;
- 2-79. $R^c = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^h = \text{CH}_3$; $R^k = 3\text{-MeOBz}$;
- 2-80. $R^a = \text{CH}_3$; $R^c = \text{CH}(3\text{-MeOBz})\text{COOH}$; $R^h = \text{Bz}$;
 $R^k = 4\text{-ClBz}$;
- 2-81. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^g = \text{CH}_3$; $R^k = 4\text{-FBz}$;
- 2-82. $R^a = \text{SCH}_3$; $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^e = \text{OCH}_3$; $R^k = \text{Bz}$;
- 2-83. $R^a = \text{CH}_3$; $R^c = \text{CH}(3\text{-FBz})\text{COOH}$; $R^k = 3\text{-ClBz}$;
- 2-84. $R^a = \text{CH}_3$; $R^b = \text{CH}_3$; $R^c = \text{CH}(2\text{-PhEt})\text{COOH}$; $R^f = \text{F}$;
 $R^k = \text{Bz}$;
- 2-85. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^h = \text{OH}$; $R^k = \text{Bz}$;
- 2-86. $R^a = \text{SCH}_3$; $R^b = \text{CH}_3$; $R^c = \text{CH}_2\text{COOH}$; $R^e = \text{OH}$;
 $R^k = \text{Bz}$;

- 2-87. $R^a = CH_3$; $R^c = CH(3-MeOBz)COOH$; $R^k = Bz$;
2-88. $R^a = CH_3$; $R^c = CH(3-ClBz)COOH$; $R^h = CH_3$;
 $R^k = 3-FBz$;
2-89. $R^b = CH(Bz)COOH$; $R^d = CH_3$; $R^f = CH_3$; $R^k = 4-NH_2Bz$;
2-90. $R^a = SCH_3$; $R^b = 4-FBz$; $R^c = CH_2COOH$; $R^k = Bz$;
2-91. $R^a = CH_3$; $R^b = CH(2-PhEt)COOH$; $R^f = OH$; $R^k = Bz$;
2-92. $R^a = F$; $R^b = CH_2CH_2COOH$; $R^e = OH$; $R^k = 4-ClBz$;
2-93. $R^c = CH(3-ClBz)COOCH_2OCOC(CH_3)_3$; $R^k = 4-MeOBz$;
2-94. $R^a = SCH_3$; $R^b = CH(2-PhEt)COOCH_2OCOC(CH_3)_3$;
 $R^k = Bz$;
2-95. $R^b = CH(4-FBz)COOCH_3$; $R^d = CH_3$; $R^k = 3-FBz$;
2-96. $R^a = SCH_3$; $R^b = CH_2COOEt$; $R^k = 3-ClBz$;
2-97. $R^b = CH(2-PhEt)COOEt$; $R^k = Bz$;
2-98. $R^a = SCH_3$; $R^b = CH_2COOCH_2CH_2OCOCH_3$; $R^k = 3-ClBz$;
2-99. $R^a = SCH_3$; $R^b = CH_2COOCH_2CH_2N(CH_3)_2$; $R^k = 3-ClBz$;
2-100. $R^c = CH(3-ClBz)COOCH_2CH_2N(CH_3)_2$; $R^k = 4-MeOBz$;
2-101. $R^b = CH(4-FBz)CONHCH_3$; $R^k = Bz$;
2-102. $R^a = CH_3$; $R^b = CH(4-FBz)CONHCH_2CH_2OH$; $R^k = Bz$;
2-103. $R^b = CH_2CONHCH_2CH_2N(CH_3)_2$; $R^k = 3-ClBz$;
2-104. $R^a = SCH_3$; $R^b = OCH_2COOH$; $R^e = CH_3$; $R^k = Bz$;
2-105. $R^b = OCH_2COOH$; $R^d = CH_3$; $R^f = CH_3$; $R^k = 3-FBz$;
2-106. $R^a = SCH_3$; $R^b = OCH(4-FBz)COOCH_2CH_2N(CH_3)_2$;
 $R^d = CH_3$; $R^k = Bz$;
2-107. $R^b = OCH_2CH_2COOH$; $R^d = CH_3$; $R^f = CH_3$; $R^k = 3-FBz$;
2-108. $R^a = CH_3$; $R^b = OCH_2CH_2COOH$; $R^k = 3,4-diMeOBz$;
2-109. $R^b = CH_2COOH$; $R^k = CO(4-Cl-Ph)$;
2-110. $R^c = CH(4-MeOBz)COOH$; $R^k = CO(2-F-Ph)$;
2-111. $R^b = CH(Ph)COOH$; $R^d = CH_3$; $R^k = COCH_3$;
2-112. $R^b = CH(CH_2COOH)$; $R^d = CH_3$; $R^k = COEt$;
2-113. $R^a = SCH_3$; $R^b = CH_2COOH$; $R^k = COEt$;
2-114. $R^b = CH_2COOH$; $R^d = CH_3$; $R^k = CH_2(thiophen-2-yl)$;
2-115. $R^b = CH_2COOH$; $R^k = CH_2(thiophen-2-yl)$;
2-116. $R^b = CH_2COOH$; $R^d = CH_3$; $R^k = CH_2(pyridin-3-yl)$;
2-117. $R^a = COOH$; $R^k = Bz$;
2-118. $R^b = COOH$; $R^k = Bz$;
2-119. $R^c = COOH$; $R^k = Bz$;
2-120. $R^d = COOH$; $R^k = Bz$;

- 2-121. $R^a = CH_3$; $R^b = COOH$; $R^k = Bz$;
2-122. $R^a = CH_3$; $R^c = COOH$; $R^k = Bz$;
2-123. $R^a = CH_3$; $R^d = COOH$; $R^k = Bz$;
2-124. $R^b = CH_2Tet$; $R^k = Bz$;
2-125. $R^a = SCH_3$; $R^b = CH_2Tet$; $R^k = Bz$;
2-126. $R^a = SCH_3$; $R^b = CH_2CH_2Tet$; $R^k = 4-FBz$;
2-127. $R^a = SCH_3$; $R^b = CH_2CH_2CH_2Tet$; $R^k = 4-FBz$;
2-128. $R^a = CH_3$; $R^b = CH_2Tet$; $R^k = Bz$;
2-129. $R^c = CH_2COOH$; $R^d = O$; $R^k = Bz$;
2-130. $R^c = CH_2COOH$; $R^d = O$;
2-131. $R^b = CH_2COOH$; $R^k = Bz$;
2-132. $R^b = CH(COOH)_2$; $R^k = Bz$.

Of these, the preferred compounds are Nos. 2-10, 2-13, 2-14, 2-19, 2-32, 2-36, 2-46, 2-57, 2-68, 2-80, 2-94, 2-100, 2-122, 2-125, 2-126 and 2-128, and the most preferred are Nos. 2-10, 2-94, 2-122.

Further examples of specific compounds of the present invention are the carbazole derivatives indicated by formula (I-3):



in which all substituent groups are as defined below,
those not mentioned being hydrogen:

- 3-1. $R^b = CH_2COOH$; $R^k = CH_3$;
- 3-2. $R^c = COOH$; $R^k = Et$;
- 3-3. $R^b = CH_2COOH$; $R^k = Et$;
- 3-4. $R^c = CH_2CH_2COOH$; $R^k = Et$;
- 3-5. $R^c = CH_2COOH$; $R^k = iBu$;
- 3-6. $R^a = CH_2COOH$; $R^k = Bz$;
- 3-7. $R^b = CH_2COOH$; $R^k = Bz$;
- 3-8. $R^c = CH_2COOH$; $R^k = Bz$;
- 3-9. $R^d = CH_2COOH$; $R^k = Bz$;
- 3-10. $R^a = SCH_3$; $R^b = CH_2COOH$; $R^k = Bz$;
- 3-11. $R^c = CH_2COOH$; $R^k = Bz$;
- 3-12. $R^a = SCH_3$; $R^b = CH_2COOH$; $R^k = Bz$;
- 3-13. $R^a = SCH_3$; $R^c = CH_2COOH$; $R^k = Bz$;
- 3-14. $R^a = SCH_3$; $R^b = CH_2COOH$; $R^d = SCH_3$; $R^k = Bz$;
- 3-15. $R^a = Et$; $R^c = CH_2COOH$; $R^k = 3-ClBz$;
- 3-16. $R^b = CH_2COOH$; $R^k = 4-ClBz$;
- 3-17. $R^a = Ph$; $R^b = CH_2COOH$; $R^k = Bz$;
- 3-18. $R^b = CH_2COOH$; $R^k = 3-FBz$;
- 3-19. $R^a = SCH_3$; $R^b = CH_2COOH$; $R^k = 4-FBz$;
- 3-20. $R^c = CH_2COOH$; $R^k = 3-MeOBz$;
- 3-21. $R^a = SCH_3$; $R^c = CH_2COOH$; $R^k = 4-MeOBz$;
- 3-22. $R^b = CH_2COOH$; $R^k = 3,4-diMeOBz$;
- 3-23. $R^b = CH(CH_3)COOH$; $R^k = Bz$;
- 3-24. $R^a = SCH_3$; $R^d = CH(Bz)COOH$; $R^k = Bz$;
- 3-25. $R^c = CH(Bz)COOH$; $R^k = Bz$;
- 3-26. $R^b = CH(Bz)COOH$; $R^e = Cl$ $R^k = Bz$;
- 3-27. $R^a = CH(Bz)COOH$; $R^h = Cl$ $R^k = Bz$;
- 3-28. $R^a = SCH_3$; $R^c = CH(3-ClBz)COOH$; $R^k = Bz$;
- 3-29. $R^b = CH(4-FBz)COOH$; $R^d = CH_3$; $R^e = OH$; $R^k = Bz$;
- 3-30. $R^c = CH(3-MeOBz)COOH$; $R^d = Ph$; $R^e = OCH_3$; $R^k = Bz$;
- 3-31. $R^b = CH(3,4-diMeOBz)COOH$; $R^e = Cl$; $R^k = Bz$;
- 3-32. $R^c = CH(3-ClBz)COOH$; $R^f = F$ $R^k = 3-ClBz$;
- 3-33. $R^a = SCH_3$; $R^c = CH(3-FBz)COOH$; $R^k = 3-ClBz$;
- 3-34. $R^c = CH(3,4-diMeOBz)COOH$; $R^k = 3-ClBz$;

- 3-35. $R^a = \text{SCH}_3$; $R^b = \text{CH}(4\text{-ClBz})\text{COOH}$; $R^k = 4\text{-ClBz}$;
3-36. $R^c = \text{CH}(3\text{-ClBz})\text{COOH}$; $R^k = 3\text{-FBz}$;
3-37. $R^a = \text{CH}_3$; $R^b = \text{CH}(4\text{-MeOBz})\text{COOH}$; $R^k = 3\text{-FBz}$;
3-38. $R^a = \text{SCH}_3$; $R^b = \text{CH}(4\text{-FBz})\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = 4\text{-FBz}$;
3-39. $R^b = \text{CH}(4\text{-MeOBz})\text{COOH}$; $R^k = 4\text{-FBz}$;
3-40. $R^c = \text{CH}(3\text{-ClBz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 4\text{-MeOBz}$;
3-41. $R^c = \text{CH}(3\text{-FBz})\text{COOH}$; $R^e = \text{OH}$; $R^k = 4\text{-MeOBz}$;
3-42. $R^c = \text{CH}(3\text{-MeOBz})\text{COOH}$; $R^f = \text{OH}$; $R^k = 4\text{-MeOBz}$;
3-43. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 3\text{-ClBz}$;
3-44. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 4\text{-ClBz}$;
3-45. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 3\text{-FBz}$;
3-46. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 3\text{-FBz}$;
3-47. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^f = \text{Cl}$; $R^k = 3\text{-FBz}$;
3-48. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 3\text{-FBz}$;
3-49. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 4\text{-FBz}$;
3-50. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^e = \text{F}$; $R^k = 4\text{-MeOBz}$;
3-51. $R^a = \text{SCH}_3$; $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 4\text{-MeOBz}$;
3-52. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 3,4\text{-diMeOBz}$;
3-53. $R^c = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = 3,4\text{-diMeOBz}$;
3-54. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 3,4\text{-diMeOBz}$;
3-55. $R^a = \text{SCH}_3$; $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = 3,4\text{-diMeOBz}$;
3-56. $R^a = \text{SCH}_3$; $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = 4\text{-NH}_2\text{Bz}$;
3-57. $R^a = \text{SCH}_3$; $R^b = \text{CH}(3\text{-PhEt})\text{COOH}$; $R^k = \text{Bz}$;
3-58. $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^f = \text{OH}$; $R^k = \text{Bz}$;
3-59. $R^a = \text{SCH}_3$; $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 3\text{-ClBz}$;
3-60. $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 3\text{-ClBz}$;
3-61. $R^c = \text{CH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^f = \text{F}$; $R^k = 4\text{-ClBz}$;
3-62. $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 3\text{-FBz}$;
3-63. $R^a = \text{SCH}_3$; $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 4\text{-FBz}$;
3-64. $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 3\text{-MeOBz}$;
3-65. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = 4\text{-MeOBz}$;
3-66. $R^a = \text{Pr}$; $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^k = 3,4\text{-diMeOBz}$;
3-67. $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $R^e = \text{OCH}_3$; $R^k = 4\text{-NH}_2\text{Bz}$;
3-68. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^e = \text{CH}_3$; $R^k = \text{Bz}$;

- 3-69. $R^b = CH_2COOH$; $R^d = CH_3$; $R^f = CH_3$; $R^k = 3-FBz$;
3-70. $R^a = CH_3$; $R^b = CH_2COOH$; $R^k = 3,4-diMeOBz$;
3-71. $R^a = SCH_3$; $R^b = CH(4-FBz)COOH$; $R^d = CH_3$;
 $R^k = Bz$;
3-72. $R^c = CH(3,4-diMeOBz)COOH$; $R^d = CH_3$; $R^k = 3-ClBz$;
3-73. $R^c = CH(3-ClBz)COOH$; $R^e = OH$; $R^k = 4-MeOBz$;
3-74. $R^a = CH_3$; $R^c = CH(Bz)COOH$; $R^f = F$; $R^k = 3-FBz$;
3-75. $R^a = SCH_3$; $R^c = CH_2COOH$; $R^f = Ph$; $R^k = Bz$;
3-76. $R^a = CH_3$; $R^c = CH(3-MeOBz)COOH$; $R^k = Bz$;
3-77. $R^b = CH(3-PhEt)COOH$; $R^d = Ph$; $R^k = Bz$;
3-78. $R^a = SCH_3$; $R^b = CH_2COOH$; $R^f = Bz$; $R^k = 4-FBz$;
3-79. $R^c = CH_2COOH$; $R^d = CH_3$; $R^h = CH_3$; $R^k = 3-MeOBz$;
3-80. $R^a = CH_3$; $R^c = CH(3-MeOBz)COOH$; $R^h = Bz$;
 $R^k = 4-ClBz$;
3-81. $R^b = CH_2COOH$; $R^d = CH_3$; $R^g = CH_3$; $R^k = 4-FBz$;
3-82. $R^a = SCH_3$; $R^c = CH(Bz)COOH$; $R^e = OCH_3$; $R^k = Bz$;
3-83. $R^a = CH_3$; $R^c = CH(3-FBz)COOH$; $R^k = 3-ClBz$;
3-84. $R^a = CH_3$; $R^b = CH_3$; $R^c = CH(3-PhEt)COOH$; $R^f = F$;
 $R^k = Bz$;
3-85. $R^a = CH_3$; $R^b = CH_2CH_2COOH$; $R^h = OH$; $R^k = Bz$;
3-86. $R^a = SCH_3$; $R^b = CH_3$; $R^c = CH_2COOH$; $R^e = OH$;
 $R^k = Bz$;
3-87. $R^a = CH_3$; $R^c = CH(3-MeOBz)COOH$; $R^k = Bz$;
3-88. $R^a = CH_3$; $R^c = CH(3-ClBz)COOH$; $R^h = CH_3$;
 $R^k = 3-FBz$;
3-89. $R^b = CH(Bz)COOH$; $R^d = CH_3$; $R^f = CH_3$; $R^k = 4-NH_2Bz$;
3-90. $R^a = SCH_3$; $R^b = 4-FBz$; $R^c = CH_2COOH$; $R^k = Bz$;
3-91. $R^c = CH(3-MeOBz)COOH$; $R^d = CH_3$; $R^f = CH_3$; $R^b = Bz$;
3-92. $R^c = CH(4-FBz)COOH$; $R^d = F$; $R^f = OH$; $R^b = Bz$;
3-93. $R^a = SCH_3$; $R^b = CH_2CH_2COOH$; $R^k = 4-FBz$;
3-94. $R^b = CH(CH_2 4-FBz)COOH$; $R^d = CH_3$; $R^k = Bz$;
3-95. $R^c = CH(CH_2 3-FBz)COOH$; $R^e = Cl$; $R^k = 3-ClBz$;
3-96. $R^c = CH(CH_2 3-ClBz)COOH$; $R^h = CH_3$; $R^k = 4-MeOBz$;
3-97. $R^a = CH_3$; $R^b = CHCH_2(3-PhEt)COOH$; $R^f = OH$;
 $R^k = Bz$;
3-98. $R^a = F$; $R^b = CH_2CH_2COOH$; $R^e = OH$; $R^k = 4-ClBz$;
3-99. $R^a = SCH_3$; $R^b = CH_2COOCH_2OCOC(CH_3)_3$; $R^k = 4-FBz$;

- 3-100. $R^b = \text{CH}(4\text{-FBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$; $R^k = \text{Bz}$;
3-101. $R^c = \text{CH}(3\text{-FBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$; $R^d = \text{CH}_3$;
 $R^k = 3\text{-ClBz}$;
3-102. $R^c = \text{CH}(3\text{-ClBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$; $R^k = 4\text{-MeOBz}$;
3-103. $R^a = \text{SCH}_3$; $R^b = \text{CH}(3\text{-PhEt})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
 $R^k = \text{Bz}$;
3-104. $R^b = \text{CH}_2\text{CH}_2\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$; $R^k = 4\text{-ClBz}$;
3-105. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOCH}_3$; $R^k = 3\text{-ClBz}$;
3-106. $R^b = \text{CH}(4\text{-FBz})\text{COOCH}_3$; $R^k = \text{Bz}$;
3-107. $R^b = \text{CH}(4\text{-FBz})\text{COOCH}_3$; $R^d = \text{CH}_3$; $R^k = 3\text{-FBz}$;
3-108. $R^b = \text{CH}(3\text{-PhEt})\text{COOCH}_3$; $R^k = \text{Bz}$;
3-109. $R^b = \text{CH}_2\text{COOEt}$; $R^k = 3\text{-ClBz}$;
3-110. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOEt}$; $R^k = 3\text{-ClBz}$;
3-111. $R^c = \text{CH}(3\text{-FBz})\text{COOEt}$; $R^k = 3\text{-ClBz}$;
3-112. $R^b = \text{CH}(4\text{-FBz})\text{COOEt}$; $R^k = 3\text{-FBz}$;
3-113. $R^b = \text{CH}(3\text{-PhEt})\text{COOEt}$; $R^d = \text{CH}_3$; $R^k = \text{Bz}$;
3-114. $R^b = \text{CH}(3\text{-PhEt})\text{COOEt}$; $R^k = \text{Bz}$;
3-115. $R^b = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{OCOCH}_3$; $R^k = 3\text{-ClBz}$;
3-116. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{OCOCH}_3$; $R^k = 3\text{-ClBz}$;
3-117. $R^c = \text{CH}(3\text{-FBz})\text{COOCH}_2\text{CH}_2\text{OCOCH}_3$; $R^k = 3\text{-ClBz}$;
3-118. $R^a = \text{CH}_3$; $R^c = \text{CH}(3\text{-ClBz})\text{COOCH}_2\text{CH}_2\text{OCOCH}_3$;
 $R^k = 4\text{-MeOBz}$;
3-119. $R^b = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $R^k = 3\text{-ClBz}$;
3-120. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $R^k = 3\text{-ClBz}$;
3-121. $R^c = \text{CH}(3\text{-FBz})\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $R^k = 3\text{-ClBz}$;
3-122. $R^c = \text{CH}(3\text{-ClBz})\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $R^k = 4\text{-MeOBz}$;
3-123. $R^b = \text{CH}_2\text{CONHCH}_3$; $R^k = 3\text{-ClBz}$;
3-124. $R^b = \text{CH}(4\text{-FBz})\text{CONHCH}_3$; $R^k = \text{Bz}$;
3-125. $R^a = \text{SCH}_3$; $R^b = \text{CH}(4\text{-FBz})\text{CONHCH}_3$; $R^k = \text{Bz}$;
3-126. $R^b = \text{CH}(4\text{-FBz})\text{CONHCH}_3$; $R^k = 3\text{-FBz}$;
3-127. $R^b = \text{CH}(3\text{-PhEt})\text{CONHCH}_3$; $R^k = \text{Bz}$;
3-128. $R^b = \text{CH}_2\text{CONHCH}_2\text{CH}_2\text{OH}$; $R^k = 3\text{-ClBz}$;
3-129. $R^b = \text{CH}(4\text{-FBz})\text{CONHCH}_2\text{CH}_2\text{OH}$; $R^k = \text{Bz}$;
3-130. $R^a = \text{CH}_3$; $R^b = \text{CH}(4\text{-FBz})\text{CONHCH}_2\text{CH}_2\text{OH}$; $R^k = \text{Bz}$;
3-131. $R^c = \text{CH}(3\text{-ClBz})\text{CONHCH}_2\text{CH}_2\text{OH}$; $R^k = 4\text{-MeOBz}$;
3-132. $R^b = \text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{OH}$; $R^k = 4\text{-ClBz}$;
3-133. $R^b = \text{CH}_2\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $R^k = 3\text{-ClBz}$;

- 3-134. $R^a = CH_3$; $R^b = CH_2CONHCH_2CH_2N(CH_3)_2$; $R^k = 3-ClBz$;
 3-135. $R^b = CH(4-FBz)CONHCH_2CH_2N(CH_3)_2$; $R^k = Bz$;
 3-136. $R^c = CH(3-ClBz)CONHCH_2CH_2N(CH_3)_2$; $R^k = 4-MeOBz$;
 3-137. $R^b = CH_2CH_2CONHCH_2CH_2N(CH_3)_2$; $R^k = 4-ClBz$;
 3-138. $R^a = SCH_3$; $R^b = OCH_2COOH$; $R^e = CH_3$; $R^k = Bz$;
 3-139. $R^b = OCH_2COOH$ $R^d = CH_3$; $R^f = CH_3$; $R^k = 3-FBz$;
 3-140. $R^a = CH_3$; $R^b = OCH_2COOH$; $R^k = 3,4-diMeOBz$;
 3-141. $R^a = SCH_3$; $R^b = OCH(4-FBz)COOH$; $R^d = CH_3$; $R^k = Bz$;
 3-142. $R^c = OCH(3,4-diMeOBz)COOH$ $R^d = CH_3$; $R^k = 3-ClBz$;
 3-143. $R^c = OCH(3-ClBz)COOH$; $R^e = OH$; $R^k = 4-MeOBz$;
 3-144. $R^a = CH_3$; $R^c = OCH(Bz)COOCH_2OCOC(CH_3)_3$; $R^f = F$;
 $R^k = 3-FBz$;
 3-145. $R^a = SCH_3$; $R^b = OCH(4-FBz)COOCH_2CH_2N(CH_3)_2$;
 $R^d = CH_3$; $R^k = Bz$;
 3-146. $R^a = SCH_3$; $R^b = OCH_2CH_2COOH$; $R^e = CH_3$; $R^k = Bz$;
 3-147. $R^b = OCH_2CH_2COOH$; $R^d = CH_3$; $R^f = CH_3$; $R^k = 3-FBz$;
 3-148. $R^a = CH_3$; $R^b = OCH_2CH_2COOH$; $R^k = 3,4-diMeOBz$;
 3-149. $R^a = SCH_3$; $R^b = OCH_2CH(4-FBz)COOH$; $R^d = CH_3$;
 $R^k = Bz$;
 3-150. $R^c = OCH(3,4-diMeOBz)CH_2COOH$; $R^d = CH_3$;
 $R^k = 3-ClBz$;
 3-151. $R^c = OCH(3-ClBz)CH_2COOH$ $R^e = OH$; $R^k = 4-MeOBz$;
 3-152. $R^a = CH_3$; $R^c = OCH_2CH(Bz)COOCH_2OCOC(CH_3)_3$;
 $R^f = F$ $R^k = 3-FBz$;
 3-153. $R^a = SCH_3$; $R^b = OCH_2CH(4-FBz)COOCH_2CH_2N(CH_3)_2$;
 $R^d = CH_3$; $R^k = Bz$;
 3-154. $R^b = CH_2COOH$; $R^d = CH_3$; $R^k = CPh$;
 3-155. $R^b = CH_2COOH$; $R^k = CO(4-Cl-Ph)$;
 3-156. $R^c = CH(3-FBz)COOH$; $R^d = CH_3$; $R^k = CO(3-F-Ph)$;
 3-157. $R^c = CH(4-MeOBz)COOH$; $R^k = CO(3-F-Ph)$;
 3-158. $R^b = CH(3-PhEt)COOH$; $R^f = Cl$; $R^k = CO(3-F-Ph)$;
 3-159. $R^b = CH(Bz)COOH$; $R^d = CH_3$; $R^k = CO(3-F-Ph)$;
 3-160. $R^c = CH(Bz)COOH$; $R^k = CO(4-F-Ph)$;
 3-161. $R^b = CH(Bz)COOH$; $R^e = F$; $R^k = CO(4-MeO-Ph)$;
 3-162. $R^a = SCH_3$; $R^b = CH(Bz)COOH$; $R^k = CPh$;
 3-163. $R^c = CH(Bz)COOH$; $R^k = CO(3,4-MeO-Ph)$;
 3-164. $R^c = CH(Bz)COOH$; $R^d = CH_3$; $R^k = CO(3,4-MeO-Ph)$;

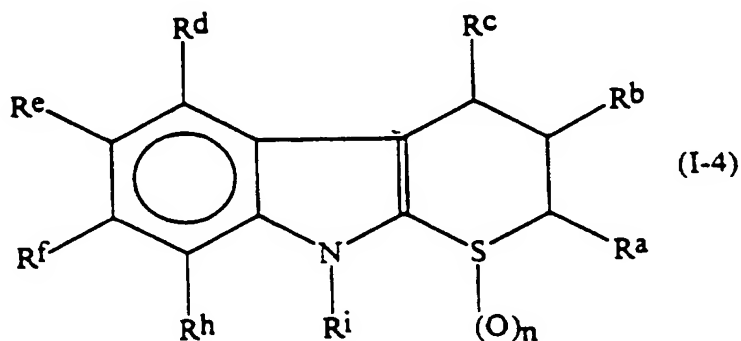
- 3-165. $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = \text{CO}(3,4\text{-MeO-Ph})$;
3-166. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{COCH}_3$;
3-167. $R^b = \text{CH}(\text{Ph})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{COCH}_3$;
3-168. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{COCH}_3$;
3-169. $R^a = \text{SCH}_3$; $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = \text{COCH}_3$;
3-170. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{COCH}(\text{CH}_3)_2$;
3-171. $R^b = \text{CH}(\text{Ph})\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{COCH}(\text{CH}_3)_2$;
3-172. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{COCH}(\text{CH}_3)_2$;
3-173. $R^a = \text{SCH}_3$; $R^b = \text{CH}(\text{Bz})\text{COOH}$; $R^k = \text{COCH}(\text{CH}_3)_2$;
3-174. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{COCH}(\text{CH}_3)_2$;
3-175. $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{COEt}$;
3-176. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{COEt}$;
3-177. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-178. $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-179. $R^c = \text{CH}(3\text{-FBz})\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-180. $R^c = \text{CH}(4\text{-MeOBz})\text{COOH}$; $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-181. $R^c = \text{CH}(4\text{-MeOBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
 $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-182. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-183. $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-184. $R^c = \text{CH}(3\text{-FBz})\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-185. $R^c = \text{CH}(4\text{-MeOBz})\text{COOH}$; $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-186. $R^c = \text{CH}(4\text{-MeOBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
 $R^k = \text{CH}_2(\text{thiophen-3-yl})$;
3-187. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{CH}_2(\text{pyridin-3-yl})$;
3-188. $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{CH}_2(\text{pyridin-3-yl})$;
3-189. $R^c = \text{CH}(3\text{-FBz})\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = \text{CH}_2(\text{pyridin-3-yl})$;
3-190. $R^c = \text{CH}(4\text{-MeOBz})\text{COOH}$; $R^k = \text{CH}_2(\text{pyridin-3-yl})$;
3-191. $R^c = \text{CH}(4\text{-MeOBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
 $R^k = \text{CH}_2(\text{pyridin-3-yl})$;
3-192. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{CH}_2(\text{pyridin-3-yl})$;
3-193. $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{CH}_2(\text{pyridin-3-yl})$;
3-194. $R^c = \text{CH}(3\text{-FBz})\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = \text{CH}_2(\text{pyridin-3-yl})$;

- 3-195. $R^C = \text{CH}(4\text{-MeOBz})\text{COOH}$; $R^k = \text{CH}_2(\text{pyridin-3-yl})$;
 3-196. $R^C = \text{CH}(4\text{-MeOBz})\text{COOCH}_2\text{OCOC}(\text{CH}_3)_3$;
 $R^k = \text{CH}_2(\text{pyridin-3-yl})$;
 3-197. $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{CH}_3$; $R^k = \text{CH}_2(\text{pyridin-4-yl})$;
 3-198. $R^b = \text{CH}_2\text{COOH}$; $R^k = \text{CH}_2(\text{pyridin-4-yl})$;
 3-199. $R^C = \text{CH}(3\text{-FBz})\text{COOH}$; $R^d = \text{CH}_3$;
 $R^k = \text{CH}_2(\text{pyridin-4-yl})$;
 3-200. $R^C = \text{CH}(4\text{-MeOBz})\text{COOH}$; $R^k = \text{CH}_2(\text{pyridin-4-yl})$;
 3-201. $R^b = \text{CH}_2\text{Tet}$; $R^k = \text{Bz}$;
 3-202. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{Tet}$; $R^k = \text{Bz}$;
 3-203. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{Tet}$; $R^k = 4\text{-FBz}$;
 3-204. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{CH}_2\text{Tet}$; $R^k = 4\text{-FBz}$;
 3-205. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{Tet}$; $R^k = \text{Bz}$;
 3-206. $R^a = \text{SCH}_3$; $R^C = \text{Tet}$; $R^k = \text{Bz}$;
 3-207. $R^a = \text{SCH}_3$; $R^d = \text{Tet}$; $R^k = (3\text{-MeO})\text{PhCH}_2$;
 3-208. $R^a = \text{SCH}_3$; $R^C = \text{CH}_2\text{Tet}$; $R^k = \text{Bz}$;
 3-209. $R^a = \text{SCH}_3$; $R^d = \text{CH}_2\text{Tet}$; $R^k = (4\text{-F})\text{PhCH}_2$;
 3-210. $R^a = \text{CH}_3$; $R^b = \text{SO}_2\text{NHCOCH}_3$; $R^k = (4\text{-F})\text{PhCH}_2$;
 3-211. $R^a = \text{SCH}_3$; $R^b = \text{SO}_2\text{NHCOCH}_3$; $R^k = \text{Bz}$;
 3-212. $R^a = \text{CH}_3$; $R^C = \text{SO}_2\text{NHCOCH}_3$; $R^k = \text{CH}_2\text{CH}_2\text{CH}_3$;
 3-213. $R^a = \text{SCH}_3$; $R^d = \text{SO}_2\text{NHCOCH}_3$; $R^k = (4\text{-Cl})\text{PhCH}_2$;
 3-214. $R^a = \text{SCH}_3$; $R^b = \text{SO}_2\text{NHCOCH}_2\text{CH}_3$; $R^k = \text{Bz}$;
 3-215. $R^a = \text{CH}_3$; $R^b = \text{SO}_2\text{NHCOCH}_2\text{CH}_3$; $R^k = (4\text{-F})\text{PhCH}_2$;
 3-216. $R^a = \text{SCH}_3$; $R^C = \text{SO}_2\text{NHCOCH}_2\text{CH}_3$; $R^k = \text{CH}_3$;
 3-217. $R^a = \text{CH}_3$; $R^d = \text{SO}_2\text{NHCOCH}_2\text{CH}_3$; $R^k = \text{Bz}$;
 3-218. $R^a = \text{CH}_3$; $R^b = \text{SO}_2\text{NHCOCH}_2\text{Ph}$; $R^k = (3,4\text{-MeO})\text{PhCH}_2$;
 3-219. $R^a = \text{SCH}_3$; $R^b = \text{SO}_2\text{NHCOCH}_2\text{Ph}$; $R^k = \text{Bz}$;
 3-220. $R^a = \text{CH}_3$; $R^C = \text{SO}_2\text{NHCOCH}_2\text{Ph}$; $R^k = \text{Bz}$;
 3-221. $R^a = \text{SCH}_3$; $R^d = \text{SO}_2\text{NHCOCH}_2\text{Ph}$; $R^k = (4\text{-Cl})\text{PhCH}_2$;
 3-222. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$; $R^k = \text{Bz}$;
 3-223. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$; $R^k = \text{Bz}$;
 3-224. $R^a = \text{SCH}_3$; $R^C = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$; $R^k = (4\text{-F})\text{PhCH}_2$;
 3-225. $R^a = \text{CH}_3$; $R^d = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$; $R^k = (4\text{-CF}_3)\text{PhCH}_2$;
 3-226. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{CH}_3$; $R^k = \text{Bz}$;
 3-227. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{CH}_3$; $R^k = \text{Bz}$;
 3-228. $R^a = \text{CH}_3$; $R^C = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{CH}_3$;
 $R^k = (4\text{-NO}_2)\text{PhCH}_2$;

- 3-229. $R^a = \text{SCH}_3$; $R^d = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{CH}_3$; $R^k = \text{Bz}$;
 3-230. $R^a = \text{SCH}_3$; $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{Ph}$; $R^k = (4\text{-F})\text{PhCH}_2$;
 3-231. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{Ph}$; $R^k = \text{Bz}$;
 3-232. $R^a = \text{SCH}_3$; $R^c = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{Ph}$; $R^k = \text{Bz}$;
 3-233. $R^a = \text{CH}_3$; $R^d = \text{CH}_2\text{SO}_2\text{NHCOCH}_2\text{Ph}$; $R^k = (4\text{-F})\text{PhCH}_2$;
 3-234. $R^b = \text{C}(\text{CH}_3)_2\text{COOH}$; $R^k = \text{Bz}$;
 3-235. $R^a = \text{SMe}$; $R^b = \text{CH}_2\text{COOH}$; $R^d = \text{n-Pr}$; $R^k = \text{Bz}$;
 3-236. $R^a = \text{SMe}$; $R^b = \text{CH}_2\text{Tet}$; $R^d = \text{n-Pr}$; $R^k = \text{Bz}$;
 3-237. $R^a = \text{SMe}$; $R^b = \text{OCH}_2\text{COOH}$; $R^d = \text{n-Pr}$; $R^k = \text{Bz}$;
 3-238. $R^a = \text{SMe}$; $R^b = \text{CH}(\text{CH}_2\text{Ph})\text{COOH}$; $R^d = \text{n-Pr}$; $R^k = \text{Bz}$.

Of these, the preferred compounds are Nos. 3-12, 3-13, 3-19, 3-32, 3-38, 3-41, 3-42, 3-57, 3-63, 3-73, 3-82, 3-86, 93, 3-101, 3-105, 3-116, 3-120, 3-140, 3-153, 3-161, 3-169, 3-179, 3-202, 3-203, 3-205, 3-212, 3-219, 3-223, 3-235, and 3-236 and the most preferred are Nos. 3-12, 3-19, 3-38, 3-73, 3-202, 3-219 and 3-236

Further examples of specific compounds of the present invention are the thiopyranoindole derivatives indicated by formula (I-4):



in which all substituent groups are as defined below,
those not mentioned being hydrogen:

- 4-1. $R^a = \text{COOH}; n = 0;$
- 4-2. $R^c = \text{COOH}; R^e = \text{CH}_3; n = 0;$
- 4-3. $R^e = \text{COOH}; n = 0;$
- 4-4. $R^f = \text{COOH}; n = 0;$
- 4-5. $R^a = \text{CH}_2\text{COOH}; n = 0;$
- 4-6. $R^b = \text{CH}_2\text{COOH}; n = 0;$
- 4-7. $R^d = \text{CH}_2\text{COOH}; n = 0;$
- 4-8. $R^a = \text{CH}_2\text{CH}_2\text{COOH}; n = 0;$
- 4-9. $R^b = \text{CH}_2\text{CH}_2\text{COOH}; n = 0;$
- 4-10. $R^c = \text{CH}_2\text{CH}_2\text{COOH}; n = 0;$
- 4-11. $R^a = \text{Tet}; n = 0;$
- 4-12. $R^b = \text{Tet}; n = 0;$
- 4-13. $R^c = \text{Tet}; n = 0;$
- 4-14. $R^a = \text{CH}_2\text{Tet}; n = 0;$
- 4-15. $R^c = \text{CH}_2\text{Tet}; n = 0;$
- 4-16. $R^a = \text{CH}_2\text{CH}_2\text{Tet}; n = 0;$
- 4-17. $R^b = \text{CH}_2\text{CH}_2\text{Tet}; R^f = \text{Cl}; n = 0;$
- 4-18. $R^b = \text{SO}_2\text{NHCOCH}_3; n = 0;$
- 4-19. $R^c = \text{SO}_2\text{NHCOCH}_3; n = 0;$
- 4-20. $R^a = \text{CH}_2\text{SO}_2\text{NHCOCH}_3; n = 0;$
- 4-21. $R^a = \text{COOH}; R^c = \text{CH}_3; n = 0;$
- 4-22. $R^b = \text{COOH}; R^c = \text{CH}_2\text{CH}_3; n = 0;$
- 4-23. $R^a = \text{CH}_3; R^c = \text{COOH}; n = 0;$
- 4-24. $R^a = \text{CH}_2\text{COOH}; R^c = \text{CH}_2\text{CH}_3; n = 0;$
- 4-25. $R^b = \text{CH}_2\text{COOH}; R^c = \text{CH}_3; R^f = \text{MeO}; n = 0;$
- 4-26. $R^b = \text{CH}_3; R^c = \text{CH}_2\text{COOH}; n = 0;$
- 4-27. $R^a = \text{CH}_2\text{CH}_2\text{COOH}; R^c = \text{CH}_3; n = 0;$
- 4-28. $R^b = \text{CH}_2\text{CH}_2\text{COOH}; R^c = \text{CH}_3; n = 0;$
- 4-29. $R^a = \text{CH}_2\text{CH}_3; R^c = \text{CH}_2\text{CH}_2\text{COOH}; n = 0;$
- 4-30. $R^a = \text{Tet}; R^c = \text{CH}_3; n = 0;$
- 4-31. $R^b = \text{Tet}; R^c = \text{CH}_2\text{Ph}; n = 0;$
- 4-32. $R^a = \text{CH}_3; R^b = \text{CH}_3; R^c = \text{Tet}; n = 0;$
- 4-33. $R^a = \text{CH}_2\text{Tet}; R^c = \text{Ph}; n = 0;$
- 4-34. $R^b = \text{CH}_2\text{Tet}; R^c = \text{CH}_3; n = 0;$

- 4-35. $R^a = \text{CH}_2\text{CH}_2\text{Ph}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_2\text{Tet}$; $R^h = \text{CH}_3$;
 $n = 0$;
- 4-36. $R^b = \text{CH}_2\text{CH}_2\text{Tet}$; $R^c = \text{CH}_3$; $n = 0$;
- 4-37. $R^a = \text{CH}_3$; $R^c = \text{CH}_2\text{CH}_2\text{Tet}$; $n = 0$;
- 4-38. $R^a = \text{SO}_2\text{NHCOCH}_3$; $R^c = \text{CH}_3$; $R^d = \text{Cl}$; $n = 0$;
- 4-39. $R^b = \text{CH}_3$; $R^c = \text{SO}_2\text{NHCOCH}_3$; $n = 0$;
- 4-40. $R^a = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$; $R^c = \text{CH}_3$; $n = 0$;
- 4-41. $R^a = \text{COOH}$; $R^c = (4\text{-F})\text{Ph}$; $n = 0$;
- 4-42. $R^b = \text{COOH}$; $R^c = (3\text{-MeO})\text{Ph}$; $n = 0$;
- 4-43. $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{Ph}$; $n = 0$;
- 4-44. $R^a = \text{CH}_2\text{CH}_2\text{COOH}$; $R^c = (4\text{-MeO})\text{Ph}$; $n = 0$;
- 4-45. $R^a = \text{Ph}$; $R^c = \text{CH}_2\text{CH}_2\text{COOH}$; $n = 0$;
- 4-46. $R^a = \text{Tet}$; $R^c = \text{Ph}$; $n = 0$;
- 4-47. $R^a = \text{CH}_2\text{Tet}$; $R^c = (3\text{-F})\text{Ph}$; $n = 0$;
- 4-48. $R^b = \text{CH}_2\text{CH}_2\text{CH}_3$; $R^c = \text{CH}_2\text{Tet}$; $n = 0$;
- 4-49. $R^a = \text{CH}_2\text{CH}_2\text{Tet}$; $R^c = (3\text{-NO}_2)\text{Ph}$; $n = 0$;
- 4-50. $R^b = \text{SO}_2\text{NHCOPh}$; $R^c = \text{Ph}$; $n = 0$;
- 4-51. $R^b = \text{CH}_2\text{SO}_2\text{NHCOPh}$; $R^c = (4\text{-NH}_2)\text{Ph}$; $n = 0$;
- 4-52. $R^a = \text{Ph}$; $R^c = \text{CH}_2\text{SO}_2\text{NHCOPh}$; $n = 0$;
- 4-53. $R^a = \text{COOH}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2\text{-(4-F)Ph}$; $n = 0$;
- 4-54. $R^b = \text{COOH}$; $R^c = (4\text{-Cl})\text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-55. $R^a = \text{Ph}$; $R^b = \text{CH}_3$; $R^c = \text{COOH}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-56. $R^a = \text{CH}_2\text{COOH}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-57. $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2\text{-(4-NH}_2)\text{Ph}$; $n = 0$;
- 4-58. $R^b = (3\text{-F})\text{Ph}$; $R^c = \text{CH}_2\text{COOH}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-59. $R^a = \text{CH}_2\text{CH}_2\text{COOH}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2\text{-(4-MeO)Ph}$; $n = 0$;
- 4-60. $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^c = (3\text{-CH}_3\text{CO})\text{Ph}$; $R^i = \text{CH}_2\text{Ph}$;
 $n = 0$;
- 4-61. $R^a = \text{Tet}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2\text{-(4-Cl)Ph}$; $n = 0$;
- 4-62. $R^b = \text{Tet}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $R^e = \text{F}$; $n = 0$;
- 4-63. $R^a = \text{Ph}$; $R^c = \text{Tet}$; $R^i = \text{CH}_2\text{-(3,4-DiMeO)Ph}$; $n = 0$;
- 4-64. $R^a = \text{CH}_2\text{Tet}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-65. $R^a = \text{CH}_2\text{CH}_2\text{Tet}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2\text{-(4-F)Ph}$; $n = 0$;
- 4-66. $R^a = \text{Ph}$; $R^c = \text{CH}_2\text{CH}_2\text{Tet}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-67. $R^a = \text{SO}_2\text{NHCOPh}$; $R^c = (3\text{-NO}_2)\text{Ph}$; $R^h = \text{NO}_2$;
 $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-68. $R^b = \text{CH}_2\text{SO}_2\text{NHCOPh}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2\text{-(4-Cl)Ph}$; $n = 0$;

- 4-69. $R^a = \text{COOH}$; $R^b = (3\text{-F})\text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-70. $R^b = \text{COOH}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2\text{-(4-NO}_2\text{)Ph}$; $n = 0$;
- 4-71. $R^a = \text{CH}_3$; $R^b = \text{Ph}$; $R^c = \text{COOH}$; $R^i = \text{CH}_2\text{-(3-F)Ph}$; $n = 0$;
- 4-72. $R^a = \text{CH}_2\text{COOH}$; $R^b = (4\text{-CH}_3\text{CONH})\text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-73. $R^a = (3\text{-F})\text{Ph}$; $R^b = \text{CH}_2\text{COOH}$; $R^i = \text{CH}_2\text{-(4-F)Ph}$; $n = 0$;
- 4-74. $R^a = \text{CH}_2\text{Ph}$; $R^b = \text{CH}_2\text{COOH}$; $R^i = \text{CH}_2\text{-(3,4-DiMeO)Ph}$;
 $n = 0$;
- 4-75. $R^a = \text{CH}_2\text{CH}_2\text{COOH}$; $R^b = \text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-76. $R^a = (4\text{-MeO})\text{Ph}$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-77. $R^a = \text{Tet}$; $R^b = \text{Ph}$; $R^i = \text{CH}_2\text{-(4-F)Ph}$; $n = 0$;
- 4-78. $R^a = \text{CH}_3$; $R^b = \text{Tet}$; $R^i = \text{CH}_2\text{-(3-MeO)Ph}$; $n = 0$;
- 4-79. $R^a = (4\text{-F})\text{Ph}$; $R^b = \text{Tet}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-80. $R^a = \text{CH}_2\text{Tet}$; $R^b = (4\text{-MeO})\text{Ph}$; $R^i = \text{CH}_2\text{-(4-F)Ph}$; $n = 0$;
- 4-81. $R^a = \text{CH}_2\text{CH}_2\text{Tet}$; $R^b = \text{Ph}$; $R^i = \text{CH}_2\text{-(3-MeO)Ph}$; $n = 0$;
- 4-82. $R^b = \text{CH}_2\text{CH}_2\text{Tet}$; $R^c = (4\text{-F})\text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-83. $R^a = \text{SO}_2\text{NHCOPh}$; $R^b = \text{Ph}$; $R^i = \text{CH}_2\text{-(2-F)Ph}$; $n = 0$;
- 4-84. $R^b = \text{CH}_2\text{SO}_2\text{NHCOPh}$; $R^c = (3\text{-Cl})\text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-85. $R^a = \text{COOH}$; $R^b = (3\text{-F})\text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-86. $R^a = \text{Ph}$; $R^b = \text{COOH}$; $R^i = \text{CH}_2\text{-(4-MeO)Ph}$; $n = 0$;
- 4-87. $R^a = \text{CH}_3$; $R^b = \text{COOH}$; $R^c = \text{CH}_2\text{CH}_2\text{CH}_3$;
 $R^i = \text{CH}_2\text{-(3-F)Ph}$; $n = 0$;
- 4-88. $R^a = \text{CH}_2\text{COOH}$; $R^b = (2\text{-Cl})\text{Ph}$; $R^i = \text{CH}_2\text{-(4-Cl)Ph}$; $n = 0$;
- 4-89. $R^a = (4\text{-MeO})\text{Ph}$; $R^b = \text{CH}_2\text{COOH}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-90. $R^a = \text{Ph}$; $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{-(3-NH}_2\text{)Ph}$; $n = 0$;
- 4-91. $R^a = \text{CH}_2\text{CH}_2\text{COOH}$; $R^b = (3,4\text{-DiMeO})\text{Ph}$; $R^f = \text{NH}_2$;
 $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-92. $R^a = \text{CH}_2\text{CH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^i = \text{CH}_2\text{-(4-F)Ph}$;
 $n = 0$;
- 4-93. $R^a = \text{Tet}$; $R^b = (4\text{-NO}_2\text{)Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-94. $R^a = \text{Ph}$; $R^b = \text{Tet}$; $R^i = \text{CH}_2\text{-(4-MeO)Ph}$; $n = 0$;
- 4-95. $R^a = \text{Tet}$; $R^b = (3\text{-Cl})\text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-96. $R^a = \text{CH}_2\text{Tet}$; $R^b = \text{Ph}$; $R^i = \text{CH}_2\text{-(4-F)Ph}$; $n = 0$;
- 4-97. $R^a = \text{CH}_2\text{CH}_2\text{Tet}$; $R^b = \text{Ph}$; $R^i = \text{CH}_2\text{-(3-F)Ph}$; $n = 0$;
- 4-98. $R^b = \text{CH}_2\text{CH}_2\text{Tet}$; $R^c = (4\text{-F})\text{Ph}$; $R^i = \text{CH}_2\text{-(4-F)Ph}$; $n = 0$;
- 4-99. $R^a = \text{SO}_2\text{NHCOPh}$; $R^b = \text{Ph}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;

- 4-100. $R^b = \text{CH}_2\text{SO}_2\text{NHCOPh}$; $R^c = \text{Ph}$; $R^i = \text{CH}_2-(3,4\text{-DiMeO})\text{Ph}$;
 $n = 0$;
- 4-101. $R^a = \text{COOH}$; $R^b = \text{CH}_3$; $R^i = \text{CH}_2-(3,4\text{-DiMeO})\text{Ph}$; $n = 0$;
- 4-102. $R^b = \text{COOH}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-103. $R^a = \text{CH}_2\text{COOH}$; $R^b = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-104. $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-105. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2-(3,4\text{-DiMeO})\text{Ph}$; $n = 0$;
- 4-106. $R^a = \text{CH}_2\text{CH}_2\text{COOH}$; $R^b = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-107. $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-108. $R^a = \text{Tet}$; $R^b = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-109. $R^a = \text{CH}_3$; $R^b = \text{Tet}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-110. $R^a = \text{CH}_3$; $R^c = \text{Tet}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-111. $R^a = \text{CH}_2\text{Tet}$; $R^b = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-112. $R^a = \text{CH}_2\text{CH}_2\text{Tet}$; $R^b = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-113. $R^b = \text{CH}_2\text{CH}_2\text{Tet}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-114. $R^a = \text{SO}_2\text{NHCOCH}_3$; $R^b = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-115. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-116. $R^a = \text{COOH}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-117. $R^a = \text{CH}_3$; $R^b = \text{COOH}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2-(3,4\text{-DiMeO})\text{Ph}$; $n = 0$;
- 4-118. $R^a = \text{CH}_3$; $R^b = \text{CH}_3$; $R^c = \text{COOH}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-119. $R^a = \text{CH}_2\text{COOH}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-120. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-121. $R^a = \text{CH}_3$; $R^b = \text{CH}_3$; $R^c = \text{CH}_2\text{COOH}$;
 $R^i = \text{CH}_2-(3,4\text{-DiMeO})\text{Ph}$; $n = 0$;
- 4-122. $R^a = \text{CH}_2\text{CH}_2\text{COOH}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-123. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-124. $R^a = \text{Tet}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-125. $R^a = \text{CH}_3$; $R^b = \text{Tet}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2-(3,4\text{-DiMeO})\text{Ph}$; $n = 0$;
- 4-126. $R^a = \text{CH}_3$; $R^b = \text{CH}_3$; $R^c = \text{Tet}$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-127. $R^a = \text{CH}_2\text{Tet}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;
- 4-128. $R^a = \text{CH}_2\text{CH}_2\text{Tet}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 0$;

- 4-129. $R^a = CH_3$; $R^b = CH_2CH_2Tet$; $R^c = CH_3$;
 $R^i = CH_2-(3,4-DiMeO)Ph$; $n = 0$;
- 4-130. $R^a = SO_2NHCOCH_3$; $R^b = CH_3$; $R^c = CH_3$;
 $R^i = CH_2Ph$; $n = 0$;
- 4-131. $R^a = CH_3$; $R^b = CH_2SO_2NHCOCH_3$; $R^c = CH_3$;
 $R^i = CH_2Ph$; $n = 0$;
- 4-132. $R^a = COOH$; $R^b = CH_3$; $R^c = CH_3$; $R^i = (3,4-DiMeO)Ph$; $n = 0$
- 4-133. $R^a = CH_3$; $R^b = COOH$; $R^c = CH_3$; $R^i = Ph$; $n = 0$;
- 4-134. $R^a = CH_3$; $R^b = CH_3$; $R^c = COOH$; $R^i = Ph$; $n = 0$;
- 4-135. $R^a = CH_2COOH$; $R^b = CH_3$; $R^c = CH_3$; $R^i = Ph$; $n = 0$;
- 4-136. $R^a = CH_3$; $R^b = CH_2COOH$; $R^c = CH_3$; $R^i = Ph$; $n = 0$;
- 4-137. $R^a = CH_3$; $R^b = CH_3$; $R^c = CH_2COOH$; $R^i = Ph$; $n = 0$;
- 4-138. $R^a = CH_2CH_2COOH$; $R^b = CH_3$; $R^c = CH_3$; $R^i = Ph$; $n = 0$;
- 4-139. $R^a = CH_3$; $R^b = CH_2CH_2COOH$; $R^c = CH_3$; $R^i = Ph$; $n = 0$;
- 4-140. $R^a = Tet$; $R^b = CH_3$; $R^c = CH_3$; $R^i = Ph$; $n = 0$;
- 4-141. $R^a = CH_2CH_3$; $R^b = Tet$; $R^c = CH_3$; $R^i = Ph$; $n = 0$;
- 4-142. $R^a = CH_3$; $R^b = CH_3$; $R^c = Tet$; $R^i = Ph$; $n = 0$;
- 4-143. $R^a = CH_2Tet$; $R^b = CH_3$; $R^c = CH_3$; $R^i = Ph$; $n = 0$;
- 4-144. $R^a = CH_2CH_2Tet$; $R^b = CH_3$; $R^c = CH_3$;
 $R^i = (3,4-DiMeO)Ph$; $n = 0$;
- 4-145. $R^a = CH_3$; $R^b = CH_2CH_2Tet$; $R^c = CH_3$; $R^i = Ph$; $n = 0$;
- 4-146. $R^a = SO_2NHCOCH_3$; $R^b = CH_3$; $R^c = CH_3$;
 $R^i = (3,4-DiMeO)Ph$; $n = 0$;
- 4-147. $R^a = CH_2CH_3$; $R^b = CH_2SO_2NHCOCH_3$; $R^c = CH_3$;
 $R^i = Ph$; $n = 0$;
- 4-148. $R^a = COOH$; $R^b = CH_3$; $R^c = CH_3$; $R^i = CH_2CH_2CH_3$; $n = 0$;
- 4-149. $R^a = CH_2CH_3$; $R^b = COOH$; $R^c = CH_3$;
 $R^i = CH_2CH_2CH_2Ph$; $n = 0$;
- 4-150. $R^a = CH_3$; $R^b = COOH$; $R^c = CH_3$;
 $R^i = CH_2CH_2CH_2CH_3$; $n = 0$;
- 4-151. $R^a = CH_2COOH$; $R^b = CH_3$; $R^c = CH_3$;
 $R^i = CH_2CH_2CH_2CH_3$; $n = 0$;
- 4-152. $R^a = CH_3$; $R^b = CH_2COOH$; $R^c = CH_2CH_3$;
 $R^i = CH_2CH_2CH_3$; $n = 0$;
- 4-153. $R^a = CH_2CH_3$; $R^b = CH_3$; $R^c = CH_2COOH$;
 $R^i = CH_2CH_2CH_3$; $n = 0$;

- 4-154. $R^a = \text{CH}_2\text{CH}_2\text{COOH}$; $R^b = \text{CH}_2\text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 0$;
- 4-155. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 0$;
- 4-156. $R^a = \text{Tet}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_2 - (3\text{-MeO})\text{Ph}$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 0$;
- 4-157. $R^a = \text{CH}_3$; $R^b = \text{Tet}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}$; $n = 0$;
- 4-158. $R^a = \text{CH}_2\text{Ph}$; $R^b = \text{Tet}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 0$;
- 4-159. $R^a = \text{CH}_2\text{Tet}$; $R^b = \text{CH}_2\text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}$; $n = 0$;
- 4-160. $R^a = \text{CH}_2\text{CH}_2\text{Tet}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_2\text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 0$;
- 4-161. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{Tet}$; $R^c = \text{CH}_2\text{Ph}$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 0$;
- 4-162. $R^a = \text{SO}_2\text{NHCOCH}_3$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2 - (4\text{-Cl})\text{Ph}$; $n = 0$;
- 4-163. $R^a = \text{CH}_2\text{Ph}$; $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 0$;
- 4-164. $R^a = \text{COOH}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 1$;
- 4-165. $R^a = \text{CH}_3$; $R^b = \text{COOH}$; $R^i = \text{CH}_2\text{Ph}$; $n = 1$;
- 4-166. $R^a = \text{CH}_2\text{CH}_3$; $R^b = \text{COOH}$; $R^i = \text{CH}_2\text{CH}_3$; $n = 1$;
- 4-167. $R^a = \text{CH}_2\text{COOH}$; $R^b = \text{CH}_2\text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{Ph}$; $n = 1$;
- 4-168. $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 1$;
- 4-169. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{Ph}$; $n = 1$;
- 4-170. $R^a = \text{CH}_2\text{CH}_2\text{COOH}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{Ph}$; $n = 1$;
- 4-171. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 1$;
- 4-172. $R^a = \text{Tet}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2 - (4\text{-F})\text{Ph}$; $n = 1$;
- 4-173. $R^a = \text{CH}_3$; $R^b = \text{Tet}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2 - (3,4\text{-DiMeO})\text{Ph}$; $n = 1$;
- 4-174. $R^a = \text{CH}_3$; $R^b = \text{CH}_3$; $R^c = \text{Tet}$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 1$;
- 4-175. $R^a = \text{CH}_2\text{Tet}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 1$;

- 4-176. $R^b = \text{CH}_2\text{Tet}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 1$;
 4-177. $R^a = \text{CH}_2\text{Tet}$; $R^i = \text{CH}_2\text{Ph}$; $n = 1$;
 4-178. $R^a = \text{CH}_2\text{CH}_2\text{Tet}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 1$;
 4-179. $R^b = \text{CH}_2\text{CH}_2\text{Tet}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 1$;
 4-180. $R^a = \text{SO}_2\text{NHCOCH}_3$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2-(3\text{-MeO})\text{Ph}$; $n = 1$;
 4-181. $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{CH}_3$; $n = 1$;
 4-182. $R^a = \text{COOH}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 2$;
 4-183. $R^a = \text{CH}_3$; $R^b = \text{COOH}$; $R^i = \text{CH}_2\text{Ph}$; $n = 2$;
 4-184. $R^a = \text{CH}_2\text{CH}_3$; $R^c = \text{COOH}$; $R^i = \text{CH}_2\text{CH}_3$; $n = 2$;
 4-185. $R^a = \text{CH}_2\text{COOH}$; $R^b = \text{CH}_2\text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{Ph}$; $n = 2$;
 4-186. $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 2$;
 4-187. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{Ph}$; $n = 2$;
 4-188. $R^a = \text{CH}_2\text{CH}_2\text{COOH}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{Ph}$; $n = 2$;
 4-189. $R^a = \text{CH}_3$; $R^b = \text{CH}_2\text{CH}_2\text{COOH}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 2$;
 4-190. $R^a = \text{Tet}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2-(4\text{-F})\text{Ph}$; $n = 2$;
 4-191. $R^a = \text{CH}_3$; $R^b = \text{Tet}$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2-(3,4\text{-DiMeO})\text{Ph}$; $n = 2$;
 4-192. $R^a = \text{CH}_3$; $R^b = \text{CH}_3$; $R^c = \text{Tet}$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 2$;
 4-193. $R^a = \text{CH}_2\text{Tet}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 2$;
 4-194. $R^b = \text{CH}_2\text{Tet}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 2$;
 4-195. $R^a = \text{CH}_2\text{Tet}$; $R^i = \text{CH}_2\text{Ph}$; $n = 2$;
 4-196. $R^a = \text{CH}_2\text{CH}_2\text{Tet}$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2\text{CH}_2\text{CH}_3$; $n = 2$;
 4-197. $R^b = \text{CH}_2\text{CH}_2\text{Tet}$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{Ph}$; $n = 2$;
 4-198. $R^a = \text{SO}_2\text{NHCOCH}_3$; $R^b = \text{CH}_3$; $R^c = \text{CH}_3$;
 $R^i = \text{CH}_2-(3\text{-MeO})\text{Ph}$; $n = 2$;
 4-199. $R^b = \text{CH}_2\text{SO}_2\text{NHCOCH}_3$; $R^c = \text{CH}_3$; $R^i = \text{CH}_2\text{CH}_3$; $n = 2$.

Of these, the preferred compounds are Nos. 4-5,

4-15, 4-35, 4-56, 4-57, 4-64, 4-68, 4-73, 4-89, 4-103, 4-104, 4-120, 4-135, 4-136, 4-143, 4-152, 4-168 and 4-193, and the most preferred are Nos. 4-56, 4-57, 4-64, 4-103, 4-135 and 4-143.

In the above, the following abbreviations are used:

iBu	isobutyl;
Bz	benzyl;
Et	ethyl;
Me	methyl;
Ph	phenyl;
Pr	propyl;
Tet	tetrazolyl.

In general, preferred compounds of the present invention are those compounds of Examples 5, 7, 9, 14, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 42, 46, 52, 61, 72, 83, 84, 86, 87, 97, 102, 103, 104, 106, 111, 114, 116, 118, 120, 130, 132, 134, 136, 137, 141, 143, 145, 149, 152, 157, 161, 163, 165, 167, 170, 172, 174, 176, 178, 180, 182, 184, 190, 200, 202, 204, 212, 214, 217, 218, 221, 222, 228, 229, 233 and 235, while the most preferred compounds are those compounds of Examples 5, 7, 9, 14, 17, 19, 21, 25, 83, 84, 86, 87, 97, 103, 116, 118, 132, 136, 137, 141, 149, 152, 161, 165, 180, 190, 200, 204, 212, 218 and 233.

Other preferred compounds are:

(9-Benzyl-1-isopropyl-4-methylcarbazol-2-yl)acetic acid;
(9-Benzyl-1-methylthio-4-trifluoromethylcarbazol-2-yl)-
acetic acid;
(9-Benzyl-4-methylthiocarbazol-3-yl)acetic acid;
(9-Benzyl-4-methyl-1-methylthiocarbazol-2-yl)acetic acid;
(9-Benzyl-3-methyl-1-methylthiocarbazol-2-yl)acetic acid;
(9-Benzyl-4-methyl-1-methoxycarbazol-2-yl)acetic acid;

(9-Benzyl-1-methyl-4-methylthiocarbazol-3-yl)acetic acid;
(9-Benzyl-1-methyl-4-methylthiocarbazol-3-yl)acetic acid;
(8-Aza-9-benzyl-4-methyl-1-methylthiocarbazol-2-yl)acetic
acid;
and pharmaceutically acceptable salts and esters thereof.

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The compounds of the present invention may be prepared by a variety of methods well known per se for the preparation of compounds of this type. For example, they may be prepared as illustrated in the following Reaction Schemes A to K.

Reaction Scheme A

Compounds of formula (I) in which R^3 represents a hydrogen atom and Y^3 represents a carboxymethyl group, that is to say compounds of formula (XIII), may be prepared as shown in the following Reaction Scheme:

In this scheme, the starting material, the compound of formula (XI), may have been prepared following the procedure described in Chem. Ber., 95, 2205 (1962).

In the above formulae, R^1 , R^2 , R^3 , Y^1 , Y^2 and Y^4 are as defined above.

Step A1:

In this step, a carboxylic acid compound of formula (XII) is prepared by the hydrolysis of a cyano compound of formula (XI).

This reaction is normally and preferably effected in the presence of a solvent, preferably an aqueous solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include:

ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; alcohols, such as methanol or ethanol; and mixtures of alcohols and water. Of these, we prefer the alcohols or a mixture of an alcohol and water.

There is likewise no particular restriction upon the nature of the base used, and any base commonly used in conventional hydrolysis reactions may equally be used here. Examples of suitable bases include: alkali metal carbonates, such as sodium carbonate, potassium carbonate or lithium carbonate; alkali metal hydroxides, such as lithium hydroxide, sodium hydroxide or potassium hydroxide; and alkaline earth metal hydroxides, such as barium hydroxide. Of these, we prefer sodium hydroxide or potassium hydroxide.

The reaction with the base can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0° to 150°C, more preferably from 25° to 100°C or at the reflux temperature of the reaction medium. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours, more preferably from 1 to 10 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method

comprises: washing the organic phase with water; separating the organic phase containing the desired compound; drying the resulting solution over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step A2:

In this step, the carboxylic acid compound of formula (XII), prepared as described in Step A1, is subjected to an Arndt-Eistert synthesis, to introduce a methylene group attached to the carboxyl group and produce a compound of formula (XIII), which may be a compound of the present invention.

In the first reaction of this step, the carboxylic acid compound of formula (XII) is first converted to its acid halide, preferably acid chloride, by reaction with a halogenating, preferably chlorinating, agent, such as oxalyl chloride, carbonyl chloride, phosphorus oxychloride or phosphorus pentachloride, preferably oxalyl chloride. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; and amides, such as formamide, dimethylformamide or dimethylacetamide. Of these, we prefer the halogenated

hydrocarbons (particularly methylene chloride) or amides (particularly dimethylformamide).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0° to 50°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours, more preferably from 1 to 12 hours will usually suffice.

In the next reaction of this step, the acid halide, preferably acid chloride, prepared as described above, is converted to the corresponding diazoketone by reaction with diazomethane. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; alcohols, such as methanol or ethanol; ketones, such as acetone or methyl ethyl ketone; and water. Of these, we prefer the alcohols (particularly methanol) or ethers (particularly diethyl ether).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is

not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0° to 50°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 to 30 hours, more preferably from 10 to 24 hours will usually suffice.

In the final reaction of this step, the diazoketone is converted to the desired compound of formula (XIII) by reaction with water in the presence of a catalyst, preferably a heavy metal catalyst, such as silver or silver oxide. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; alcohols, such as methanol or ethanol; ketones, such as acetone or methyl ethyl ketone; and water. Of these, we prefer the alcohols (particularly methanol).

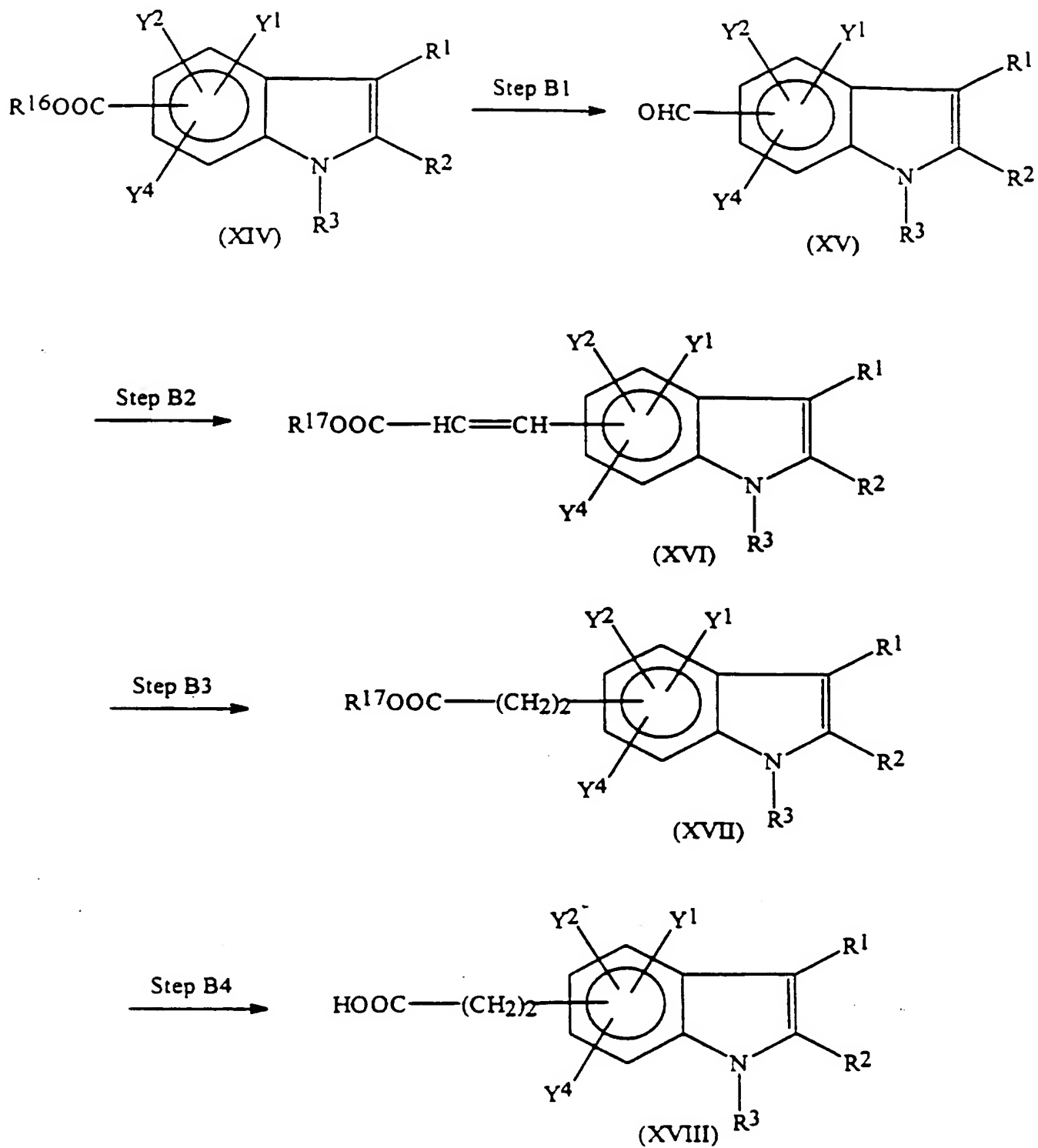
The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to

carry out the reaction at a temperature of from 10° to 150°C, more preferably at the reflux temperature of the reaction medium. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 20 hours, more preferably from 3 to 10 hours will usually suffice.

After completion of any or all of the above reactions, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: washing the organic phase with water; separating the organic phase containing the desired compound; drying the resulting solution over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Reaction Scheme B

Compounds of formula (I) in which R^3 preferably represents a hydrogen atom and Y^3 represents a 2-carboxyethyl group, that is to say compounds of formula (XVIII), may be prepared as shown in the following Reaction Scheme:

Reaction Scheme B

In the above formulae, R^1 , R^2 , R^3 , Y^1 , Y^2 and Y^4 are as defined above, and R^{16} and R^{17} are the same or different and each represents a carboxy-protecting group.

There is no particular restriction on the nature of the carboxy-protecting group represented by R^{16} and R^{17} , and any carboxy-protecting group known in the art may equally be used in this reaction. Examples of such groups which may be used in this reaction include those protecting groups defined and exemplified above in relation to the carboxy-protecting groups which may be represented by Y^1 , etc.

Step B1:

In this step, the compound of formula (XIV) is reduced to a formyl compound of formula (XV).

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents are non-polar. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane; aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; and alcohols, such as methanol or ethanol. Of these, we prefer the alcohols (particularly methanol), halogenated hydrocarbons (particularly methylene chloride) and the ethers (particularly tetrahydrofuran).

There is likewise no particular restriction upon the

nature of the reducing agent used, and any reducing agent commonly used in conventional reactions may equally be used here. Examples of suitable reducing agents include sodium borohydride, lithium aluminum hydride, diisobutylaluminum hydride, lithium aluminum tri-*t*-butoxyhydride and lithium aluminum trimethoxyhydride.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -78° to 50°C, more preferably from -60° to 25°C and most preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, preferably 10 minutes to 12 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means

as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step B2:

In this step, a compound of formula (XVI) is prepared by a Wittig reaction from a compound of formula (XV), which may have been prepared by the procedure described in step B1.

The compound of formula (XV) is reacted with a Wittig reagent, in this case preferably an alkyl or aralkyl di(alkyl or aryl)phosphonoacetate under conditions conventional for this type of reaction. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; nitriles, such as acetonitrile or isobutyronitrile; amides, such as formamide, dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; and sulfoxides, such as dimethyl sulfoxide or sulfolane. Of these, we prefer tetrahydrofuran.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0 to 80°C, more preferably from 0 to 20°C. The time required for the reaction may also vary widely,

depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 5 hours, more preferably from 10 minutes to 30 minutes, will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water or an aqueous solution; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step B3:

In this step, the carbon-carbon double bond in the compound of formula (XVI), which may have been prepared as described in Step B2, is reduced to a carbon-carbon single bond, to produce the compound of formula (XVII).

Any reduction process commonly used for this type of reaction may be employed here, although a catalytic reduction process is preferred. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least

to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; and alcohols, such as methanol or ethanol. Of these, we prefer the alcohols (particularly methanol) and the ethers (particularly tetrahydrofuran).

There is likewise no particular restriction upon the nature of the catalyst used, and any catalyst commonly used in conventional reactions may equally be used here. Examples of suitable catalysts include palladium, palladium-on-charcoal, platinum or Raney nickel.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20° to 40°C , more preferably from 0° to 25°C , most preferably about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, more preferably from 10 minutes to 12 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: filtering off the catalyst employed and then distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such

conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step B4:

In this step, the compound of formula (XVII) is hydrolysed to remove the carboxy-protecting group R¹⁷ and give the desired compound of formula (XVIII). The reaction is normally and preferably effected in the presence of a base.

This reaction is also normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as tetrahydrofuran, dioxane or dimethoxyethane; alcohols, such as methanol or ethanol; and mixtures of alcohols and water. Of these, we prefer the alcohols or a mixture of an alcohol and water.

There is likewise no particular restriction upon the nature of the base used, and any base commonly used in conventional reactions of this type may equally be used here. Examples of suitable bases include: alkali metal carbonates, such as sodium carbonate, potassium carbonate or lithium carbonate; and alkali metal hydroxides, such as sodium hydroxide, potassium hydroxide or lithium hydroxide, or alkaline earth metal hydroxides, such as barium hydroxide. Of these, we prefer sodium hydroxide or potassium hydroxide.

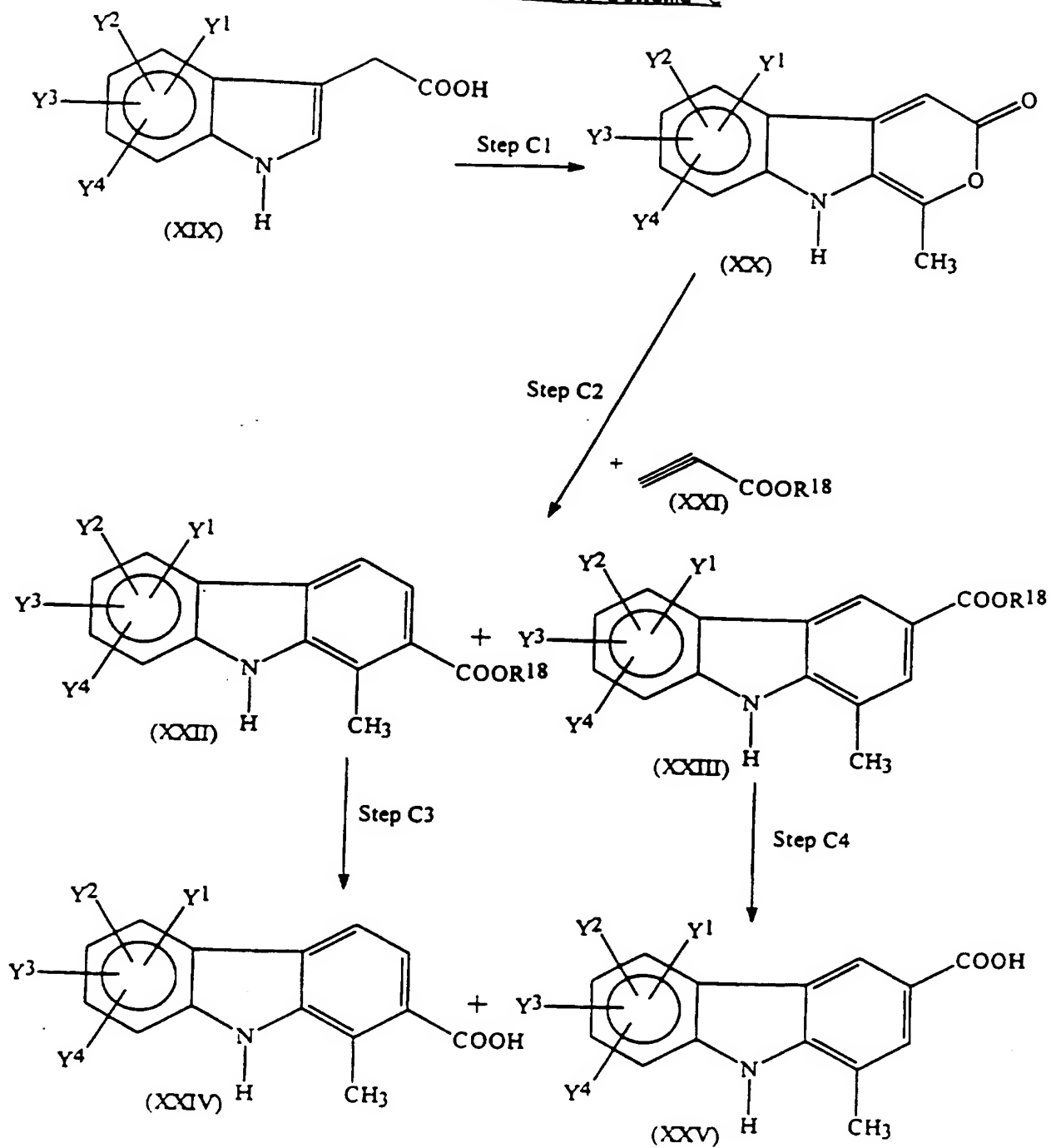
The reaction with the base can take place over a wide range of temperatures, and the precise reaction

temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0° to 150°C, more preferably from 10° to 50°C, and most preferably about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours, more preferably from 1 to 10 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water or with an appropriate aqueous solution; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired product thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Reaction Scheme C

In this reaction scheme, a compound of formula (XXIV) or (XXV) is prepared.

Reaction Scheme C

In the above formulae, Y^1 , Y^2 , Y^3 and Y^4 are as defined above, and R^{18} represents a carboxy-protecting group, for example as defined and exemplified above.

Step C1:

In this step, the compound of formula (XIX) is reacted with acetic anhydride in the presence of a Lewis acid, to prepare a compound of formula (XX).

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Non-polar solvents are preferred. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane; aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; and alcohols, such as methanol or ethanol. Of these, we prefer the halogenated hydrocarbons (particularly methylene chloride) and the ethers (particularly diethyl ether).

There is likewise no particular restriction upon the nature of the Lewis acid used, and any Lewis acid commonly used in conventional reactions may equally be used here. Examples of suitable Lewis acids include boron trifluoride, boron trifluoride diethyl etherate, titanium tetrachloride and stannic chloride.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is

not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0°C to the boiling temperature of the reaction medium, more preferably from 30°C to the boiling temperature of the reaction medium. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 10 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water or with an appropriate aqueous solution; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired product thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step C2:

In this step, the compound of formula (XX), which may have been prepared as described in Step C1, is reacted with a propiolate of formula (XXI) in a Diels-Alder reaction, to give a mixture of compounds of

formulae (XXII) and (XXIII).

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Non-polar solvents are preferred. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane; aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; and alcohols, such as methanol or ethanol. Of these, we prefer the alcohols (particularly methanol), halogenated hydrocarbons (particularly methylene chloride), the ethers (particularly tetrahydrofuran) and the aromatic hydrocarbons (particularly xylene).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0°C to the boiling temperature of the reaction medium, more preferably from 30°C to the boiling temperature of the reaction medium. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 10 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises removing the solvent by distillation, preferably in vacuo, to leave the desired product, which can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

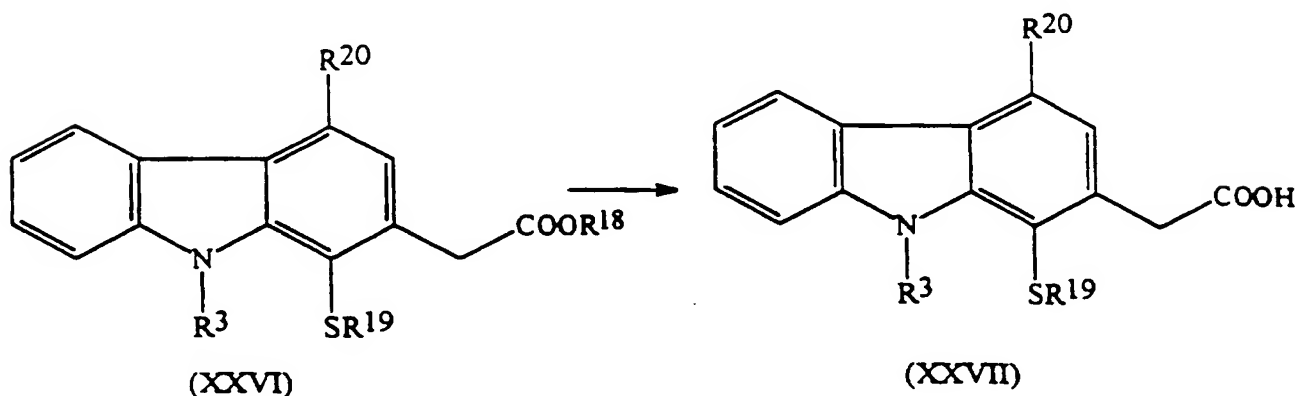
The compounds of formulae (XXII) and (XXIII) may be separated at this stage or they may be used as a mixture in steps C3 and C4.

Steps C3 and C4:

In these steps the compounds of formulae (XXII) and (XXIII) are hydrolysed to give compounds of formulae (XXIV) and (XXV), respectively. The reaction involved in this Step is essentially the same as that involved in Step B4 of Reaction Scheme B, and may be carried out using the same reagents and reaction conditions.

Reaction Scheme D

In this scheme, a compound of formula (XXVI), which may have been prepared following the procedures described in Chem. Pharm. Bull., 29, 1601 (1981), is hydrolysed, to give a compound of formula (XXVII):



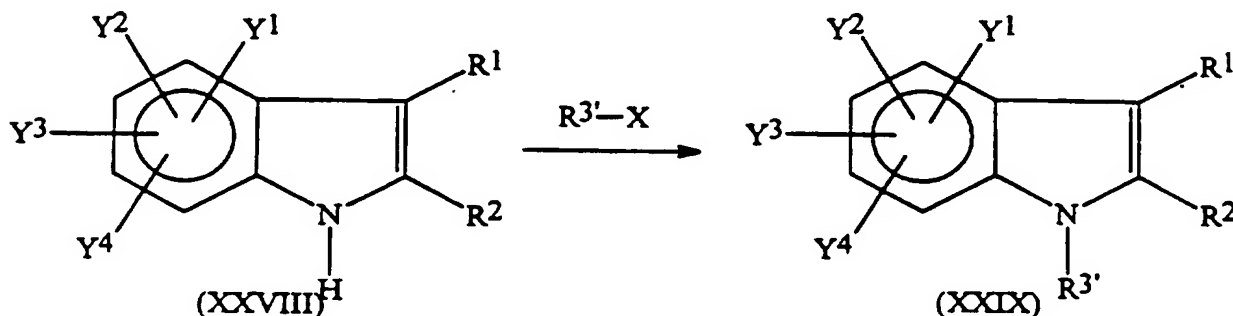
In the above formulae, R³ and R¹⁸ are as defined above; and R¹⁹ and R²⁰ are the same or different and each represents an alkyl group having from 1 to 6 carbon atoms. Examples of such alkyl groups include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, hexyl and isohexyl groups. Of these, we prefer those alkyl groups having from 1 to 4 carbon atoms, preferably the methyl, ethyl, propyl, isopropyl, butyl and isobutyl groups, and most preferably the methyl group.

The reaction involved in this Step is essentially the same as that involved in Step B4 of Reaction Scheme

B, and may be carried out using the same reagents and reaction conditions.

Reaction Scheme E

In this scheme, a compound of formula (XXVIII), which is a compound of formula (I) in which R^3 represents a hydrogen atom, is converted to a compound of formula (XXIX), which is a compound of formula (I) in which R^3 represents an amino-protecting group, particularly an alkyl, aralkyl or acyl group:



In the above formulae, R^1 , R^2 , Y^1 , Y^2 , Y^3 and Y^4 are as defined above; $R^{3'}$ represents an alkyl, aralkyl or acyl group (as defined and exemplified above in relation to R^3); and X represents a leaving group.

This reaction involves reacting a compound of formula (XXVIII) with a suitable amount, for example from 1 to 4 equivalents (more preferably from 2 to 3 equivalents) of a compound of formula: $R^{3'}$ -X (where $R^{3'}$ and X are as defined above) in a solvent in the presence or absence of a base, but preferably in the presence of a base.

There is no particular limitation upon the nature of the leaving group represented by X, provided that it is a group capable of leaving as a nucleophilic residue, such as are well known in the art. Examples of preferred leaving groups include: halogen atoms, such as the chlorine, bromine and iodine atoms; lower alkoxy-carbonyloxy groups, such as the methoxycarbonyloxy and ethoxycarbonyloxy groups; halogenated alkylcarbonyloxy groups, such as the chloroacetoxy, dichloroacetoxy, trichloroacetoxy and trifluoroacetoxy groups; lower alkanesulfonyloxy groups, such as the methanesulfonyloxy and ethanesulfonyloxy groups; lower haloalkanesulfonyloxy groups, such as the trifluoromethanesulfonyloxy and pentafluoroethanesulfonyloxy groups; and arylsulfonyloxy groups, such as the benzenesulfonyloxy, *p*-toluenesulfonyloxy and *p*-nitrobenzenesulfonyloxy groups. Of these, we prefer the halogen atoms, lower haloalkanesulfonyloxy groups and arylsulfonyloxy groups.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane and heptane; aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and dichlorobenzene; esters, such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate and diethyl carbonate; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; nitriles, such as acetonitrile and isobutyronitrile; and amides, such as formamide, dimethylformamide, dimethylacetamide, *N*-methyl-2-

pyrrolidone, N-methylpyrrolidinone and hexamethylphosphoric triamide. Of these, we prefer the ethers (particularly dimethoxyethane or tetrahydrofuran) and the amides (particularly dimethylformamide).

There is likewise no particular restriction upon the nature of the base used, and any base commonly used in conventional reactions of this type may equally be used here. Examples of suitable bases include: alkali metal hydrides, such as lithium hydride, sodium hydride or potassium hydride; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide, potassium *t*-butoxide or lithium methoxide; and organic metal bases, such as butyllithium or lithium diisopropylamide. Of these, we prefer the alkali metal hydrides (particularly lithium hydride or sodium hydride).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20° to 60°C, more preferably from 0°C to 20°C, for alkylation or aralkylation, and from -78°C to room temperature, more preferably from -78°C to 0°C, for acylation. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, more preferably from 5 minutes to 6 hours will usually suffice.

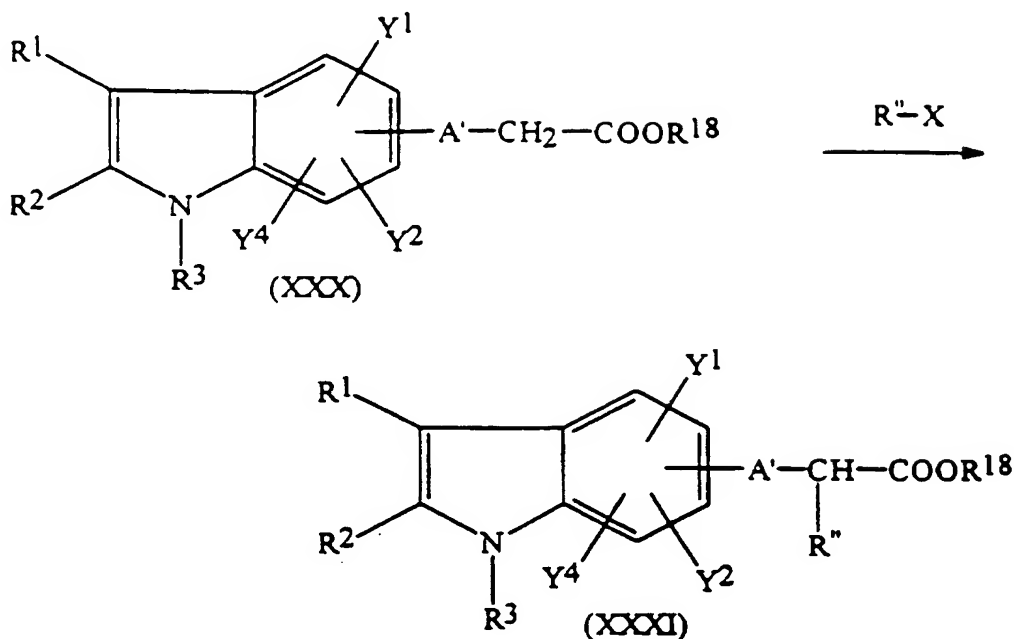
After completion of the reaction, the desired compound can be recovered from the reaction mixture by

conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Alternatively, where $R^{3'}$ represents an acyl group, the compound of formula $R^{3'}-X$ may be replaced by the corresponding anhydride of formula $R^{3''}-O-R^{3''}$ (where $R^{3''}$ represents an acyl group). This reaction may take place in the presence or absence of a base and is carried out under the same conditions, including solvent, temperatures and time, as described above.

Reaction Scheme F

In this scheme, an alkyl or aralkyl group, as defined and exemplified above in relation to substituents γ , is introduced into a compound of formula (XXX), to give a compound of formula (XXXI):



In the above formulae, R^1 , R^2 , R^3 , Y^1 , Y^2 , and Y^4 are as defined above; R'' represents an alkyl or aralkyl group, as defined and exemplified above in relation to substituents γ , A' represents an unsubstituted alkylene or oxyalkylene group having one fewer carbon atom than the corresponding group in the compound of formula (I); and R^{18} and X are as defined and exemplified above. The reaction preferably takes place in the presence of a base.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane;

amides, such as dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; and sulfoxides, such as dimethyl sulfoxide or sulfolane. Of these, we prefer the ethers (particularly tetrahydrofuran or dimethoxyethane) and the amides (particularly dimethylformamide).

There is likewise no particular restriction upon the nature of the base used, and any base commonly used in conventional reactions may equally be used here. Examples of suitable bases include: alkali metal hydrides, such as lithium hydride, sodium hydride or potassium hydride; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide, potassium t-butoxide or lithium methoxide; and organic metal bases, such as butyllithium or lithium diisopropylamide. Of these, we prefer the alkali metal hydrides (particularly lithium hydride or sodium hydride).

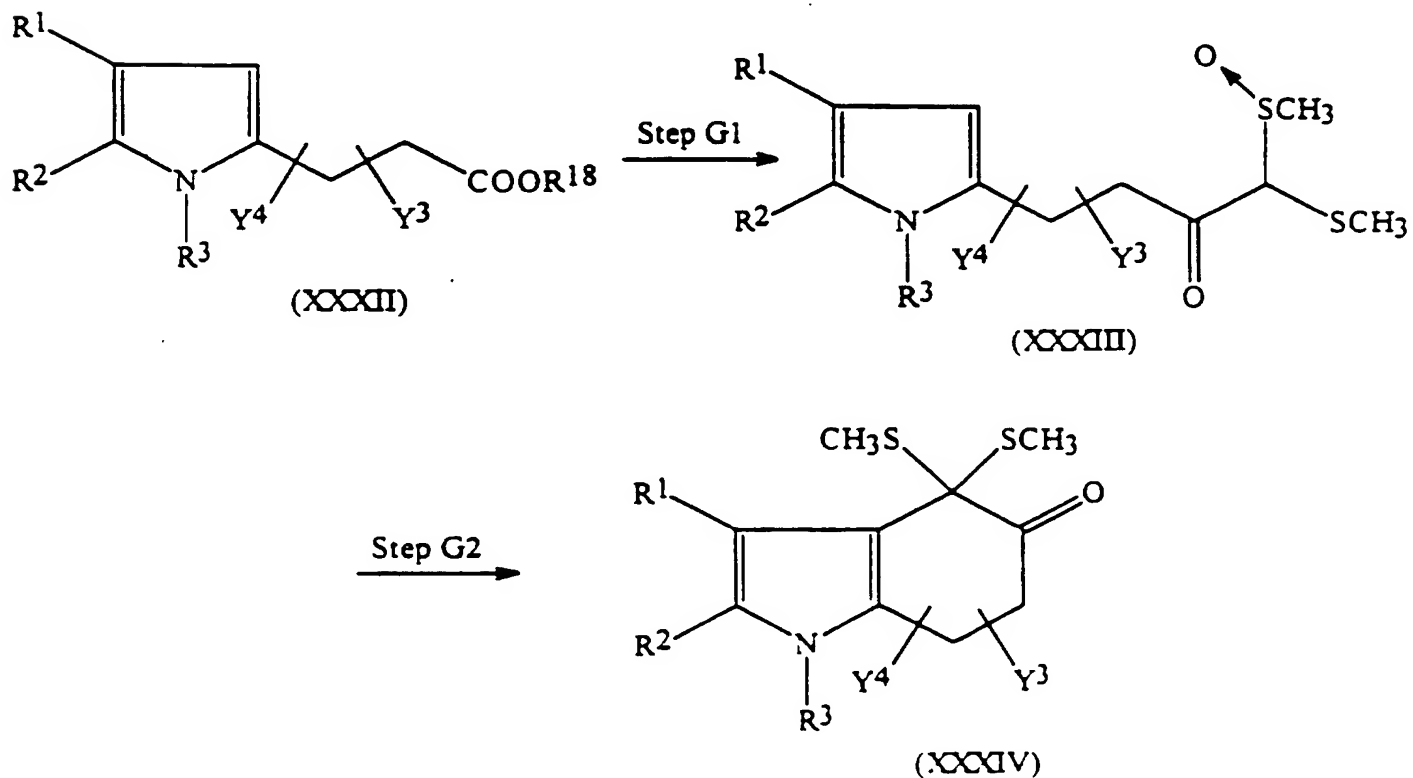
The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20° to 60°C, more preferably from 0°C to 20°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, more preferably from 5 minutes to 6 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by

conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Reaction Scheme G

This reaction scheme produces an indole derivative having two methylthio groups at the 4-position and an oxo group at the 5-position, which may be a useful starting material for the preparation of some of the compounds of the present invention:



In the above formulae, R^1 , R^2 , R^3 , Y^3 , and Y^4 are as defined above.

Step G1:

In this step, a compound of formula (XXXII) is reacted with methyl methylsulfinylmethyl sulfide, to give a compound of formula (XXXIII).

This reaction preferably takes place in the presence of an acid. There is no particular restriction upon the nature of the acid used, and any acid commonly used in conventional reactions may equally be used here. Examples of suitable acids include: Lewis acids, such as boron trifluoride, boron trifluoride diethyl etherate, titanium tetrachloride and stannic chloride; mineral acids, especially hydrohalic acids (such as hydrofluoric acid, hydrobromic acid, hydroiodic acid or hydrochloric acid), nitric acid, carbonic acid, sulfuric acid or phosphoric acid; lower alkylsulfonic acids, such as methanesulfonic acid, trifluoromethanesulfonic acid or ethanesulfonic acid; arylsulfonic acids, such as benzenesulfonic acid or p-toluenesulfonic acid; and organic carboxylic acids, such as acetic acid or benzoic acid.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents are non-polar. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; amides, such as dimethylformamide, dimethylacetamide or hexamethylphosphoric

triamide; and sulfoxides, such as dimethyl sulfoxide or sulfolane. Of these, we prefer the ethers (particularly tetrahydrofuran or dimethoxyethane) and the amides (particularly dimethylformamide).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -78°C to the reflux temperature of the reaction medium, more preferably from 0°C to the reflux temperature of the reaction medium. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 24 hours, more preferably from 30 minutes to 6 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step G2:

In this step, a compound of formula (XXXIII) is cyclised by treatment with an acid, to give a compound of formula (XXXIV).

This reaction takes place in the presence of an acid. There is no particular restriction upon the nature of the acid used, and any acid commonly used in conventional reactions may equally be used here. Examples of suitable acids include: Lewis acids, such as boron trifluoride, boron trifluoride diethyl etherate, titanium tetrachloride and stannic chloride; mineral acids, especially hydrohalic acids (such as hydrofluoric acid, hydrobromic acid, hydroiodic acid or hydrochloric acid), nitric acid, carbonic acid, sulfuric acid or phosphoric acid; lower alkylsulfonic acids, such as methanesulfonic acid, trifluoromethanesulfonic acid or ethanesulfonic acid; arylsulfonic acids, such as benzenesulfonic acid or p-toluenesulfonic acid; and organic carboxylic acids, such as acetic acid or benzoic acid.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents are non-polar. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; amides, such as dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; and sulfoxides, such as dimethyl sulfoxide or sulfolane. Of these, we prefer the ethers (particularly tetrahydrofuran or dimethoxyethane) and the amides

(particularly dimethylformamide).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0°C to 200°C, more preferably from about room temperature to 150°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 24 hours, more preferably from 30 minutes to 6 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Reaction Scheme H

Compounds containing a carboxyl group can be converted to the corresponding compounds containing a tetrazolylmethyl group by the following reactions:

Step H1:

In this step, the carboxylic acid compound is reacted with a cyano compound (preferably an alkali metal cyanide, such as sodium cyanide or potassium cyanide, or a trialkylsilyl cyanide in which the alkyl parts have from 1 to 6 carbon atoms, such as trimethylsilyl cyanide) in an inert solvent. When the trialkylsilyl cyanide is employed, the Q-trialkylsilyl derivative thus obtained is then treated with an acid, to give a desired cyanomethyl compound.

When an alkali metal cyanide is employed, it is preferably used in an amount of from 1 to 3 equivalents, more preferably from 1.2 to 2 equivalents per mole of the carboxylic acid compound. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; alcohols, such as methanol or ethanol; water; or a mixture of water and one or more of these organic solvents. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -10°C to 80°C, more preferably from 0°C to 30°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions

outlined above, a period of from 1 to 24 hours, more preferably from 2 to 16 hours, will usually suffice. This reaction can, if desired, be accelerated by adding sodium hydrogen sulfite. After completion of the reaction, the product can be recovered by conventional means, for example by extracting the reaction mixture with a water-immiscible organic solvent (such as ethyl acetate) and evaporating the solvent from the extract. If necessary, the resulting product can be further purified by conventional means, such as recrystallization or the various chromatography techniques, notably column chromatography.

If a trialkylsilyl cyanide is employed, it is preferably used in an amount of from 1 to 2 equivalents, more preferably from 1.05 to 1.2 equivalents, per mole of the carboxylic acid compound, and the reaction is preferably carried out in the presence of a catalytic amount of zinc iodide. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; and halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride and chloroform. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -10°C to 80°C , more preferably from 10°C to 40°C . The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the

reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours, more preferably from 1 to 16 hours, will usually suffice. After completion of the reaction, the desired cyano compound, in the form of its Q-trialkylsilyl derivative, can be obtained by concentrating the reaction mixture, extracting the concentrate with a water-immiscible organic solvent, washing the extract with a weakly alkaline aqueous solution, such as aqueous sodium hydrogencarbonate, and evaporating off the solvent. If necessary, the resulting product can be further purified by conventional means, such as recrystallization or the various chromatography techniques, notably column chromatography.

The Q-trialkylsilyl group is then removed. This reaction can be carried out by treatment with a catalytic amount of an acid (for example p-toluene-sulfonic acid, methanesulfonic acid or hydrochloric acid) in a suitable solvent, the nature of which is not critical, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include alcohols, such as methanol or ethanol. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -20°C to 60°C, more preferably around room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 5 hours, more preferably from 30 minutes to 2 hours, will usually suffice.

The product of this step is a compound in which the carboxyl group of the original compound has been replaced by a cyanomethyl group, i.e. it contains one more carbon atom than the original compound.

After completion of the reaction, the product can be recovered from the reaction mixture by conventional means, for example: by concentrating the reaction mixture, extracting the concentrate with a water-immiscible organic solvent, such as ethyl acetate, washing with a weakly alkaline aqueous solution, such as aqueous sodium hydrogencarbonate, and evaporating off the solvent. If necessary, the resulting product can be further purified by conventional means, such as recrystallization or the various chromatography techniques, notably column chromatography.

Step H2:

This step is an alternative to step H1 and produces a cyano compound containing the same number of carbon atoms as the original carboxylic acid compound.

In the first part of this step, the carboxylic acid compound is converted to a corresponding carbamoyl compound by reaction of the carboxylic acid compound (or an active derivative thereof, for example a lower alkyl ester, e.g. methyl ester, acid halide, e.g. chloride, or acid anhydride, which can be prepared by well known methods) with ammonia.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable

solvents include: ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; alcohols, such as methanol or ethanol; ketones, such as acetone or methyl ethyl ketone; and water. Of these, we prefer the alcohols (particularly methanol).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 10°C to 50°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 hour to 10 days, more preferably from 10 hours to 8 days, will usually suffice.

The resulting carbamoyl compound is then dehydrated, to give a cyano compound.

This reaction may be conducted by reacting the corresponding carbamoyl compound with a dehydrating agent, preferably an acid anhydride, such as acetic anhydride, trifluoroacetic anhydride, methanesulfonic anhydride or trifluoromethanesulfonic anhydride, or thionyl chloride. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons, such as benzene, toluene, xylene and heptane; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene

chloride and chloroform; ethers, such as diethyl ether, tetrahydrofuran and dioxane; and esters, such as ethyl acetate and butyl acetate. The reaction is effected in the presence of an organic amine, preferably triethylamine, pyridine or *N*-methyldmorpholine.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -10°C to 100°C, more preferably from 0°C to 50°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 16 hours, more preferably from 30 minutes to 6 hours, will usually suffice.

After completion of the reaction, the product can be recovered by adding a weakly basic aqueous solution (such as an aqueous solution of sodium hydrogencarbonate) and a water-immiscible organic solvent, such as ethyl acetate, to the reaction mixture, separating the resulting organic solvent layer and distilling off the solvent. The product may then, if necessary, be further purified by conventional means, for example, by recrystallization, or by the various chromatography techniques, notably by column chromatography.

Step H3:

In this step, a tetrazolylmethyl or tetrazolyl compound is prepared by converting the cyano group contained in the cyanomethyl compound, obtained as described in step H1, or the cyano compound, obtained as described in step H2, to a tetrazolyl group. This step

can be carried out using any of the following three reactions.

Reaction (a): Reaction with an alkali metal azide

This reaction is carried out by reacting the corresponding cyanomethyl or cyano compound with a suitable amount, for example from 1 to 5 equivalents, more preferably from 1 to 3 equivalents, of an alkali metal azide, such as lithium azide, sodium azide or potassium azide, preferably sodium azide, in the presence of an ammonium halide. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as dioxane or 1,2-dimethoxyethane; alcohols, such as methanol or ethanol; amides, such as dimethylformamide or dimethylacetamide; and sulfoxides, such as dimethyl sulfoxide. The amount of ammonium halide is preferably from 0.5 to 2 equivalents, more preferably from 1 to 1.2 equivalents, per mole of the cyanomethyl or cyano compound. Examples of suitable ammonium halides include ammonium fluoride, ammonium chloride and ammonium bromide, preferably ammonium chloride.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 70°C to 150°C, more preferably from 90°C to 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent

employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 hours to 7 days, more preferably from 1 to 5 days will usually suffice.

After completion of the reaction, the product may be recovered from the reaction mixture by conventional means. For example, water and a water-immiscible organic solvent, such as ethyl acetate, are added to the reaction mixture, and the organic solvent layer is separated, after which the solvent is evaporated off, to give the product. If necessary, the resulting product can be further purified by conventional means, such as recrystallization or the various chromatography techniques, notably column chromatography.

Reaction (b): Reaction with a trialkyl or triaryltin azide

This reaction is carried out by reacting the cyano cyano compound with a suitable amount, for example from 1 to 3 equivalents, more preferably from 1 to 2 equivalents, of a trialkyltin azide or a triaryltin azide. Examples of trialkyltin azides include those in which each alkyl group has from 1 to 6 carbon atoms, such as trimethyltin azide, triethyltin azide or tributyltin azide. Examples of triaryltin azides include triphenyltin azide and tritolyltin azide. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons, such as benzene, toluene, xylene or heptane; halogenated hydrocarbons, such as dichloroethane or chloroform; ethers, such as

dioxane or 1,2-dimethoxyethane; esters, such as ethyl acetate or butyl acetate; amides, such as dimethylformamide or dimethylacetamide; and sulfoxides, such as dimethyl sulfoxide. The resulting tin adduct is then treated with an acid (preferably hydrochloric acid or sulfuric acid), a base (preferably an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide, an alkali metal carbonate, such as sodium carbonate or potassium carbonate, or an alkali metal hydrogencarbonate, such as sodium hydrogencarbonate or potassium hydrogencarbonate) or an alkali metal fluoride (preferably sodium fluoride or potassium fluoride). The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: those solvents described above; alcohols, such as methanol or ethanol; water; and aqueous alcohols.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction with the tin compound at a temperature of from 60°C to 150°C, more preferably from 80°C to 120°C, and the treatment with the acid, base or fluoride at around room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 8 hours to 7 days, more preferably from 1 to 5 days will usually suffice for the reaction with the tin compound, whilst the treatment with the acid,

base or fluoride will normally require from 30 minutes to 24 hours, more preferably from 1 to 6 hours.

After completion of the reaction, the product may be recovered from the reaction mixture by conventional means. For example, water and a water-immiscible organic solvent, such as ethyl acetate, are added to the reaction mixture, and the organic solvent layer is separated, after which the solvent is evaporated off, to give the product. If necessary, the resulting product can be further purified by conventional means, such as recrystallization or the various chromatography techniques, notably column chromatography.

Reaction (c): Reaction with a trialkyl or triaryltin halide and an alkali metal azide

This reaction is carried out in the same manner as in Reaction (b), except that a suitable amount, for example from 1 to 3 equivalents, more preferably from 1 to 2 equivalents, of a trialkyl or triaryltin halide (for example trimethyltin chloride, triethyltin chloride, tributyltin chloride or triphenyltin chloride) and a suitable amount, for example from 1 to 3 equivalents, more preferably from 1 to 2 equivalents, of an alkali metal azide (preferably sodium azide or potassium azide) are used in place of the trialkyl or triaryltin azide.

After completion of the reaction, the product may be recovered from the reaction mixture by conventional means. For example, water and a water-immiscible organic solvent, such as ethyl acetate, are added to the reaction mixture, and the organic solvent layer is separated, after which the solvent is evaporated off, to give the product. If necessary, the resulting product can be further purified by conventional means, such as

recrystallization or the various chromatography techniques, notably column chromatography.

Reaction Scheme I

Compounds containing a carboxyalkyl group can be converted to the corresponding α -hydroxycarbonyl compounds by α -hydroxylation of the carboxyl moiety by reacting the carboxyalkyl containing compound with a base and, subsequently, molecular oxygen (preferably oxygen gas).

There is no particular restriction upon the nature of the base used, and any base commonly used in conventional α -hydroxylation reactions may be used. Examples of suitable bases include the organic metal bases, such as butyllithium, lithium diisopropylamide, sodium hexamethyldisilazide and lithium hexamethyldisilazide (which may be prepared following the procedures described in US-A-4,347,375). Of these, we prefer sodium hexamethyldisilazide or lithium hexamethyldisilazide (particularly lithium hexamethyldisilazide).

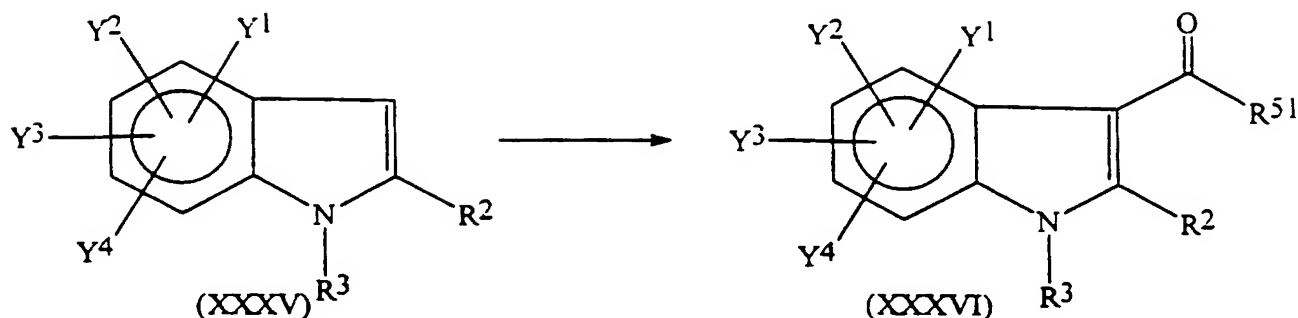
The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents are non-polar. Example of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane. of these, we prefer the ethers, particularly tetrahydrofuran.

The reaction can take place over a wide range of

temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20°C to 100°C , more preferably from about 0°C to 50°C .

The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period from 10 minutes to 24 hours, more preferably from 30 minutes to 60 hours, will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the resulting solution over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallisation, reprecipitation or one of the various chromatography techniques, notably column chromatography.

Reaction Scheme J

In the above formulae, R², R³, Y¹, Y², Y³ and Y⁴ are as defined above, and R⁵¹ represents a methyl group or a hydrogen atom.

Step J:

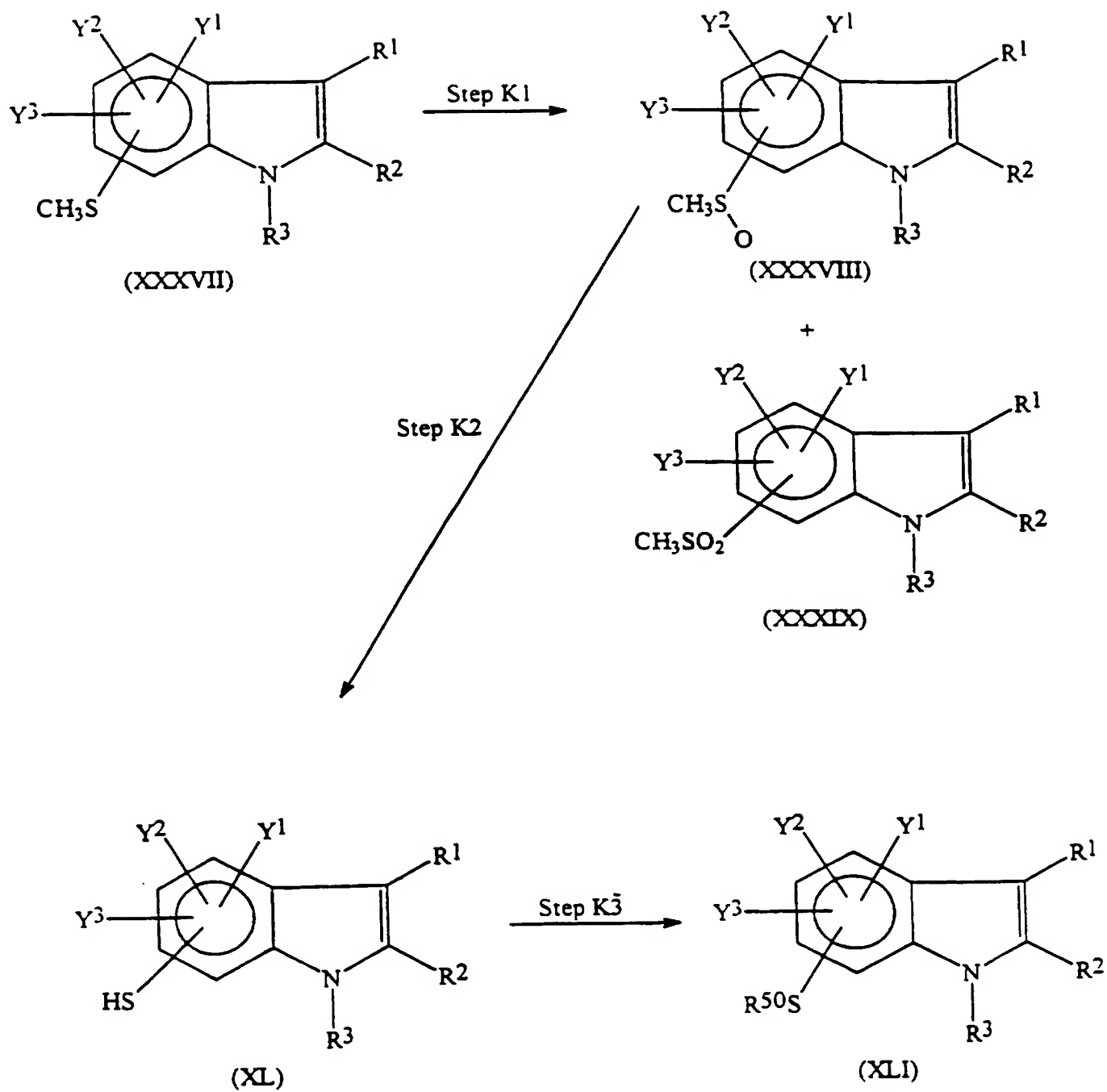
In this step, an acetyl compound of formula (XXXVI) is prepared from an indole compound of formula (XXXV) by a Vilsmeier reaction using oxyphosphorylchloride and dimethylformamide or dimethylacetamide.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect either on the reaction or on the reagents involved, and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane; halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; and amides, such as formamide, di-

methylformamide or dimethylacetamide. We prefer to use dimethylformamide or dimethylacetamide as the solvent, especially as these compounds are also reactants.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent and the starting materials. However, in general, we find it convenient to carry out the reaction at a temperature of from -20°C to 200°C , more preferably from 0°C to 100°C , and most preferably at about 5° to 10°C . The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, where the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, preferably 10 minutes to 12 hours, is usually sufficient.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and removing the solvent by evaporation under reduced pressure. The thus obtained compound can, if required, be further purified by such conventional means as recrystallization, reprecipitation or any of the various chromatography techniques, especially column chromatography.

Reaction Scheme K

In the above formulae, R^1 , R^2 , R^3 , Y^1 , Y^2 and Y^3 are as defined above, R^{50} represents an alkyl group having from 1 to 6 carbon atoms, and X represents a leaving group.

Step K1:

In this step, the methylthio group of the compound of formula (XXXVII) is oxidized to a sulfinyl or sulfonyl group of a compound of formula (XXXVIII) or (XXXIX), respectively.

Any oxidation process commonly used for this type of reaction may be employed here, although a catalytic oxidation process is preferred.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect either on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents are non-polar, and examples of suitable solvents include: aliphatic hydrocarbons, such as hexane; aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; and alcohols, such as methanol or ethanol. We prefer to use halogenated hydrocarbons or ethers as solvents, particularly methylene chloride or tetrahydrofuran.

There is likewise no particular restriction upon the nature of the catalyst used, and any catalyst commonly used in conventional reactions may equally be used here. An example of a suitable catalyst is

m-chloroperbenzoic acid.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -78° to 80°C , more preferably from 0° to 50°C , and most preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, where the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, preferably about 10 minutes to 12 hours, is usually sufficient.

After the reaction has been allowed to go to completion, the target compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and removal of the solvent by evaporation under reduced pressure. The target compound can, if required, then be further purified by such conventional means as recrystallization, reprecipitation or any of the various chromatography techniques, especially column chromatography.

Step K2:

In this step, a compound of formula (XL) is prepared from a compound of formula (XXXVIII) or (XXXIX) by a Pummerer rearrangement, as described in Tetrahedron Letters vol.25, No.17, 1753 (1984). The compound of formula (XXXVIII) or (XXXIX) may be prepared by the procedure described in step K1 above.

The compound of formula (XXXVIII) or (XXXIX) is reacted with a strong carboxylic acid anhydride, in this case preferably a trihalogenated acetic anhydride, such as trifluoroacetic anhydride, under conditions conventional for this type of reaction. The reaction mixture is then suitably dried, such as by treatment with anhydrous magnesium sulfate, and then hydrolyzed. Hydrolysis may be effected either with an alcohol, such as methanol or ethanol, or with an acidic aqueous solution, such as an aqueous acetic acid.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect either on the reaction or on the reagents involved, and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; nitriles, such as acetonitrile or isobutyronitrile; amides, such as formamide, dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; and sulfoxides, such as dimethyl sulfoxide or sulfolane. Of these, we prefer the halogenated hydrocarbons, such as methylene chloride.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -50°C to 80°C , more preferably from 0 to 30°C , and most preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, where the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 5 hours, more preferably from 10 minutes to 30 minutes, is usually sufficient.

After the reaction has been allowed to go to completion, the target compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water or an aqueous solution; separating the organic phase containing the target compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The target compound can, if required, then be further purified by such conventional means as recrystallization, reprecipitation or any of the various chromatography techniques, especially column chromatography.

Step K3:

This reaction involves reacting a compound of formula (XL) with a compound of formula $\text{R}^{50}\text{-X}$ (where R^{50} and X are as defined above) to obtain a compound of formula (XLI). A suitable amount of the compound of formula R^{50}X is, for example, from 1 to 4 equivalents

(more preferably from 2 to 3 equivalents), and is preferably in a solvent in the presence or absence of a base, but preferably in the presence of a base.

There is no particular limitation upon the nature of the leaving group represented by X, provided that it is a group capable of leaving as a nucleophilic residue, such as are well known in the art. Examples of preferred leaving groups include: halogen atoms, such as chlorine, bromine and iodine atoms; lower alkoxy-carbonyloxy groups, such as the methoxycarbonyloxy and ethoxycarbonyloxy groups; halogenated alkylcarbonyloxy groups, such as the chloroacetoxy, dichloroacetoxy, trichloroacetoxy and trifluoroacetoxy groups; lower alkanesulfonyloxy groups, such as the methanesulfonyloxy and ethanesulfonyloxy groups; lower haloalkanesulfonyloxy groups, such as the trifluoromethanesulfonyloxy and pentafluoroethanesulfonyloxy groups; and arylsulfonyloxy groups, such as the benzenesulfonyloxy, p-toluenesulfonyloxy and p-nitrobenzenesulfonyloxy groups. Of these, we prefer the halogen atoms, lower haloalkanesulfonyloxy groups and arylsulfonyloxy groups.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect either on the reaction or on the reagents involved, and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane and heptane; aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and dichlorobenzene; esters, such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate and diethyl carbonate; ethers, such as diethyl ether,

diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; nitriles, such as acetonitrile and isobutyronitrile; and amides, such as formamide, dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone and hexamethylphosphoric triamide. We prefer to use ethers or amides as solvents, particularly dimethoxyethane, tetrahydrofuran or dimethylformamide.

There is no particular limitation upon the nature of the base used, and any base which can be used in conventional reactions of this type may equally be used here. Examples of preferred bases include organic bases, such as N-methylemorpholine, triethylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-(1-pyrrolidinyl)pyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di-t-butyl-4-methylpyridine, quinoline, N,N-dimethylaniline and N,N-diethylaniline. If desired, a catalytic amount of 4-(N,N-dimethylamino)pyridine, 4-(1-pyrrolidinyl)pyridine or a combination of other bases can be used. In order to promote the reaction, a quaternary ammonium salt (such as benzyltriethylammonium chloride or tetrabutylammonium chloride) or a crown ether (such as dibenzo-18-crown-6) may be added to the reaction system.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out any alkylation or aralkylation reaction at a temperature of from -20° to 60°C, more preferably from 0°C to 20°C. We find it convenient to carry out any acylation reaction at a temperature of from -78°C to room temperature, more preferably from -78°C to 0°C.

The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, where the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, more preferably from 5 minutes to 6 hours, is usually sufficient.

After the reaction has been allowed to go to completion, the target compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the target compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The target compound can, if required, then be further purified by such conventional means as recrystallization, reprecipitation or any of the various chromatography techniques, especially column chromatography.

Alternatively, Steps K2 and K3 can be executed as a "one-pot" reaction. Thus, after the reaction with a strong carboxylic acid anhydride, a suitable hydrolyzing agent, $R^{50}-X$ and base are all added to the reaction mixture at once. The reaction is carried out under similar conditions, including solvent, temperatures and time, to those described above.

The preparation of various of the compounds of the present invention is illustrated in the following non-limiting Examples.

M&C FOLIO: 545P72553/FP-9509

WANGDOC: 1122D

EXAMPLE 1tert-Butyl (2-hydroxy-1,1-bismethylthio-1,2,3,4-tetrahydrocarbazol-2-yl)acetate1(a) Methyl 3-(indol-3-yl)propionate

36.2 g of powdered potassium carbonate was added, with ice-cooling, to a solution of 24.8 g of 3-(indol-3-yl)propionic acid in 500 ml of N,N-dimethylformamide, followed by the addition of a solution of 10.2 ml methyl iodide in 50 ml of N,N-dimethylformamide. The reaction mixture was then warmed to room temperature and stirred for 3 hours. After this time, ice water was added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate. The organic extract was then washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 500 g of silica gel with a 4 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 25.8 g of the title compound as an amorphous solid.

1(b) 3-(4-Methylthio-4-methylsulfinyl-3-oxobuten-1-yl)-indole

A solution of 11.2 g of methyl methylsulfinyl sulfide in tetrahydrofuran was added, with ice-cooling, to a suspension of 13.1 g of sodium hydride (55% w/w dispersion in mineral oil) in 100 ml of tetrahydrofuran. The reaction mixture was then heated to room temperature and stirred for 2 hours. A solution of 12.2 g of methyl 3-(indol-3-yl)propionate, as obtained in Example 1(a) above, in 50 ml of tetrahydrofuran was subsequently added to the reaction mixture, which was next refluxed for 2

hours, and then acidified by the addition of a 1N aqueous solution of hydrochloric acid. The aqueous layer was extracted with ethyl acetate, and the resulting organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The residue thus obtained was subjected to column chromatography using 400 g of silica gel with a 1 : 2 v/v mixture of hexane and ethyl acetate as the eluent, to yield 16.8 g of the title compound as an amorphous solid.

1(c) 1,1-Bismethylthio-1,2,3,4-tetrahydrocarbazol-3-one

680 mg of p-toluenesulfonic acid was added to a mixture of 10.6 g of 3-(4-methylthio-4-methylsulfinyl-3-oxobutene-1-yl)indole, as obtained in Example 1(b), in 150 ml of tetrahydrofuran and 40 ml of benzene. The reaction mixture was next refluxed for 3 hours and then neutralized by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The solvent was removed from the resulting mixture by evaporation under reduced pressure and ethyl acetate was added to the residue. The aqueous layer was then extracted with ethyl acetate, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 300 g of silica gel with a 9 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 9.7 g of the title compound as an amorphous solid.

1(d) tert-Butyl (2-hydroxy-1,1-bismethylthio-1,2,3,4-tetrahydrocarbazol-2-yl)acetate

53 ml of a 1.7 M solution of n-butyllithium in hexane was added at a temperature of -78°C to a solution of 13.9 g of diisopropylamine in 50 ml of toluene. The reaction mixture was then warmed to 0°C and stirred for

15 minutes. The reaction mixture was then cooled to -78°C , and a solution of 5.0 g of 1,1-bismethylthio-1,2,3,4-tetrahydrocarbazol-3-one, as obtained in Example 1(c), in 10 ml of toluene was added to the cooled solution. The reaction mixture was next stirred for 30 minutes and then heated to room temperature and stirred for 2 hours. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with toluene, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 250 g of silica gel with benzene as the eluent, to yield 6.8 g of the title compound as an amorphous solid.

EXAMPLE 2

tert-Butyl (1-methylthiocarbazol-2-yl)acetate

2.5 ml of glacial acetic acid was added to a solution of 3.37 g of tert-butyl (2-hydroxy-1,1-bis-methylthio-1,2,3,4-tetrahydrocarbazol-2-yl)acetate, as obtained in Example 1, in 40 ml of xylene. The reaction mixture was subsequently refluxed for 1 hour and then neutralized by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 80 g of silica gel with a 19 : 1 v/v mixture of benzene and ethyl acetate as the eluent, to yield 2.40 g of the title compound, melting at 137°C .

138°C, 50 mg of 2-hydroxy-1-methylthiocarbazole (melting at 138 - 140°C), 85 mg of tert-butyl (2-hydroxy-1-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)acetate (melting at 156 - 157°C) and 125 mg of 3,3a,4,5,10,10b-hexahydro-3a-hydroxy-10b-methylthiofuro[2,3-a]carbazol-2-one (obtained as an amorphous solid).

The Nuclear Magnetic Resonance Spectrum [(CDCl₃, 270MHz), δ ppm] results for each of the above compounds are as follows:

tert-Butyl (1-methylthiocarbazol-2-yl)acetate

1.46 (9H, singlet);
2.36 (3H, singlet);
4.05 (2H, singlet);
7.21 (1H, doublet, J = 7.8Hz);
7.24 (1H, triplet, J = 7.9Hz);
7.42 (1H, triplet, J = 7.9Hz);
7.49 (1H, doublet, J = 7.9Hz);
7.99 (1H, doublet, J = 7.9Hz);
8.04 (1H, doublet, J = 7.8Hz);
8.62 (1H, broad singlet).

2-Hydroxy-1-methylthiocarbazole

2.33 (3H, singlet);
6.77 (1H, singlet);
6.93 (1H, doublet, J = 8.4Hz);
7.22 (1H, triplet, J = 7.7Hz);
7.36 (1H, triplet, J = 7.7Hz);
7.45 (1H, doublet, J = 7.7Hz);
7.94 (1H, doublet, J = 8.4Hz);
7.96 (1H, doublet, J = 7.7Hz);
8.39 (1H, broad singlet).

tert-Butyl (2-hydroxy-1-oxo-1,2,3,4-tetrahydro-

carbazol-2-yl)acetate

1.49 (9H, singlet);
2.3 - 2.5 (2H, multiplet);
2.60 (1H, doublet, $J = 14.6\text{Hz}$);
2.69 (1H, doublet, $J = 14.6\text{Hz}$);
3.02 (1H, doubled doublet of doublets,
 $J = 5.1, 8.7, 17.4\text{Hz}$);
3.23 (1H, triplet of doublets, $J = 5.1, 17.4\text{Hz}$);
4.59 (1H, singlet);
7.1 - 7.2 (1H, multiplet);
7.3 - 7.5 (2H, multiplet);
7.66 (1H, doublet, $J = 7.9\text{Hz}$);
8.81 (1H, broad singlet).

3,3a,4,5,10,10b-Hexahydro-3a-hydroxy-10b-methylthiofuro-
[2,3-a]carbazol-2-one

2.08 (3H, singlet);
2.12 (1H, doubled doublet of doublets,
 $J = 5.9, 9.9, 13.9\text{Hz}$);
2.27 (1H, doubled doublet of doublets,
 $J = 3.3, 5.9, 13.9\text{Hz}$);
2.70 (1H, doublet, $J = 16.8\text{Hz}$);
2.74 (1H, doubled doublet of doublets,
 $J = 5.9, 9.9, 17.2\text{Hz}$);
2.78 (1H, doublet, $J = 16.8\text{Hz}$);
3.02 (1H, doubled doublet of doublets,
 $J = 3.3, 5.9, 17.2\text{Hz}$);
3.17 (1H, singlet);
7.14 (1H, triplet, $J = 7.6\text{Hz}$);
7.28 (1H, triplet, $J = 7.6\text{Hz}$);
7.38 (1H, doublet, $J = 7.6\text{Hz}$);
7.53 (1H, doublet, $J = 7.6\text{Hz}$);
8.40 (1H, broad singlet).

EXAMPLE 3(1-Methylthiocarbazol-2-yl)acetic acid

5 ml of formic acid was added to 51 mg of tert-butyl (1-methylthiocarbazol-2-yl)acetate, as obtained in Example 2. The reaction mixture was then warmed to room temperature and stirred for 4 hours. Formic acid was next removed under reduced pressure, and the residue was recrystallized from ethyl acetate and hexane, to yield 44 mg of the title compound, melting at 210 - 212°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.36 (3H, singlet);
4.20 (2H, singlet);
7.22 (1H, doublet, $J = 7.9\text{Hz}$);
7.2 - 7.3 (1H, multiplet);
7.44 (1H, triplet, $J = 7.6\text{Hz}$);
7.48 (1H, triplet, $J = 7.6\text{Hz}$);
8.01 (1H, doublet, $J = 7.9\text{Hz}$);
8.04 (1H, doublet, $J = 7.6\text{Hz}$);
8.63 (1H, broad singlet).

EXAMPLE 4tert-Butyl (9-benzyl-1-methylthiocarbazol-2-yl)acetate

A solution of 98 mg of tert-butyl (1-methylthiocarbazol-2-yl)acetate, as obtained in Example 2, in 1 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 13 mg of sodium hydride (55% w/w dispersion in mineral oil) in 2 ml of N,N-dimethylformamide. 51 mg of benzyl bromide was added to the reaction mixture which was then stirred for 1 hour. After this time, a saturated aqueous solution of

ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate and the organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 4 g of silica gel with a 1 : 2 v/v mixture of hexane and benzene as the eluent, to yield 120 mg of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.43 (9H, singlet);
1.98 (3H, singlet);
4.09 (2H, singlet);
6.35 (2H, singlet);
7.03 (2H, doublet, $J = 6.5\text{Hz}$);
7.1-7.5 (7H, multiplet);
8.08 (2H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 5

(9-Benzyl-1-methylthiocarbazol-2-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl (9-benzyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 4, as starting material, the title compound was obtained in quantitative yield, melting at 182 - 183°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.95 (3H, singlet);
4.22 (2H, singlet);
6.34 (2H, singlet);

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7.03 (2H, doublet, $J = 7.7\text{Hz}$);
7.1-7.5 (7H, multiplet);
8.0-8.2 (2H, multiplet).

EXAMPLE 6

tert-Butyl [9-(4-chlorobenzyl)-1-methylthio- carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using 4-chlorobenzyl chloride as starting material, the title compound was obtained as an oil in a yield of 96%.

EXAMPLE 7

[9-(4-Chlorobenzyl)-1-methylthiocarbazol-2-yl]acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(4-chlorobenzyl)-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 6, as starting material, the title compound was obtained in quantitative yield, melting at $176 - 178^{\circ}\text{C}$.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.01 (3H, singlet);
4.23 (2H, singlet);
6.30 (2H, singlet);
6.96 (2H, doublet, $J = 8.4\text{Hz}$);
7.1-7.4 (5H, multiplet);
7.43 (1H, triplet, $J = 7.6\text{Hz}$);
8.0-8.2 (2H, multiplet).

EXAMPLE 8tert-Butyl [9-(4-fluorobenzyl)-1-methylthio-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using 4-fluorobenzyl bromide as starting material, the title compound was obtained as an oil in a yield of 98%.

EXAMPLE 9[9-(4-Fluorobenzyl)-1-methylthiocarbazol-2-yl]acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(4-fluorobenzyl)-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 8, as starting material, the title compound was obtained in quantitative yield, melting at 156 - 157°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz);

δ ppm:

- 2.00 (3H, singlet);
- 4.22 (2H, singlet);
- 6.30 (2H, singlet);
- 6.8-7.1 (4H, multiplet);
- 7.2-7.4 (3H, multiplet);
- 7.43 (1H, triplet, J = 8.0Hz);
- 8.08 (1H, doublet, J = 7.8Hz);
- 8.10 (1H, doublet, J = 7.9Hz).

EXAMPLE 10tert-Butyl [9-(4-nitrobenzyl)-1-methylthiocarbazol-2-yl]-
acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using 4-nitrobenzyl bromide as starting material, the title compound was obtained as an oil in a yield of 94%.

EXAMPLE 11[9-(4-Nitrobenzyl)-1-methylthiocarbazol-2-yl]acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(4-nitrobenzyl)-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 10, as starting material, the title compound was obtained in quantitative yield as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.02 (3H, singlet);
4.21 (2H, singlet);
6.41 (2H, singlet);
7.17 (2H, doublet, $J = 8.5\text{Hz}$);
7.2-7.4 (5H, multiplet);
7.44 (1H, triplet, $J = 7.5\text{Hz}$);
8.0-8.2 (4H, multiplet).

EXAMPLE 12

tert-Butyl (9-benzyl-1-methylthiocarbazol-2-yl)-
hydroxyacetate

0.47 ml of a 1.0 M solution of lithium hexamethyl-disilazide in tetrahydrofuran was added, with ice-cooling, to a solution of 65 mg of tert-butyl (9-benzyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 4, in 5 ml of tetrahydrofuran. The reaction mixture was then stirred for 1 hour in the presence of atmospheric oxygen. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 1.5 g of silica gel with a 3 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 43 mg of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),
δ ppm:

1.34 (9H, singlet);
2.09 (3H, singlet);
3.69 (1H, broad singlet);
6.23 (1H, singlet);
6.37 (2H, singlet);
7.01 (2H, doublet, J = 7.8Hz);
7.1-7.5 (7H, multiplet);
8.09 (1H, doublet, J = 7.9Hz);
8.13 (1H, doublet, J = 8.0Hz).

EXAMPLE 13Benzyl (9-benzyl-4-methyl-1-methylthiocarbazol-2-yl)-
acetate

a) Following a procedure and using relative proportions of starting materials similar to those described in Examples 1 and 2, but using 3-(indol-3-yl)butyric acid as starting material, benzyl (4-methyl-1-methylthiocarbazol-2-yl)acetate was obtained, and was used without further purification in the next step.

b) A solution of 2.42 g of benzyl (4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in a) above, in 40 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 280 mg of sodium hydride (55% w/w dispersion in mineral oil) in 30 ml of N,N-dimethylformamide. 1.1 g of benzyl bromide was next added to the reaction mixture which was then stirred for 1 hour. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 80 g of silica gel with a 1 : 2 v/v mixture of hexane and benzene as the eluent, to yield 2.7 g of the title compound, as an oil, and 195 mg of benzyl 2-(4-methyl-1-methylthiocarbazol-2-yl)-3-phenylpropionate, also as an oil.

EXAMPLE 14(9-Benzyl-4-methyl-1-methylthiocarbazol-2-yl)acetic acid

50 ml of ethanol and 50 ml of a 2N aqueous solution of sodium hydroxide was added to 1.16 g of benzyl (9-benzyl-4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 13 a). The reaction mixture was stirred for 2 hours at room temperature, after which time it was acidified by adding a 1N aqueous solution of hydrochloric acid and then concentrated by evaporation under reduced pressure. Ethyl acetate was added to the residue thus obtained. The aqueous layer was extracted with ethyl acetate and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 20 g of silica gel with a 1 : 1 v/v mixture of hexane and ethyl acetate as the eluent, and then recrystallized from ethyl acetate and hexane, to yield 0.90 g of the title compound, melting at 219 - 220°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

- 1.96 (3H, singlet);
- 2.89 (3H, singlet);
- 4.15 (1H, singlet);
- 6.40 (2H, singlet);
- 7.0-7.5 (9H, multiplet);
- 8.19 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 152-(4-Methyl-1-methylthiocarbazol-2-yl)-3-phenylpropionic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using benzyl 2-(4-methyl-1-methylthiocarbazol-2-yl)-3-phenylpropionate, as obtained in Example 13, as starting material, the title compound was obtained in a yield of 93%, melting at 186 - 187°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

- 2.16 (3H, singlet);
- 2.91 (3H, singlet);
- 3.11 (1H, doublet of doublets, $J = 7.5, 13.7\text{Hz}$);
- 3.53 (1H, doublet of doublets, $J = 7.5, 13.7\text{Hz}$);
- 5.18 (1H, triplet, $J = 7.5\text{Hz}$);
- 7.1-7.6 (9H, multiplet);
- 8.17 (1H, doublet, $J = 7.9\text{Hz}$);
- 8.70 (1H, broad singlet).

EXAMPLE 16tert-Butyl 2-(9-benzyl-1-methylthiocarbazol-2-yl)-3-phenylpropionate

A solution of 826 mg of tert-butyl (1-methylthiocarbazol-2-yl)acetate, as obtained in Example 2, in 5 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 220 mg of sodium hydride (55% w/w dispersion in mineral oil) in 10 ml of N,N-dimethylformamide. 855 mg of benzyl bromide was then added to the reaction mixture which was then warmed to room temperature and stirred for 1 hour. After this time, a

saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate and the organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 30 g of silica gel with a 1 : 2 v/v mixture of hexane and benzene as the eluent, to yield 1.21 g of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.30 (9H, singlet);
1.89 (3H, singlet);
2.99 (1H, doublet of doublets, $J = 7.2, 13.7\text{Hz}$);
3.41 (1H, doublet of doublets, $J = 8.0, 13.7\text{Hz}$);
5.23 (1H, doublet of doublets, $J = 7.2, 8.0\text{Hz}$);
6.31 (2H, singlet);
6.9-7.5 (14H, multiplet);
8.07 (1H, doublet, $J = 7.7\text{Hz}$);
8.13 (1H, doublet, $J = 8.2\text{Hz}$).

EXAMPLE 17

2-(9-Benzyl-1-methylthiocarbazol-2-yl)-3-phenylpropionic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl 2-(9-benzyl-1-methylthiocarbazol-2-yl)-3-phenylpropionate, as obtained in Example 16, as starting material, the title compound was obtained in a yield of 99%, melting at 154 - 156°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.86 (3H, singlet);
3.06 (1H, doublet of doublets, J = 7.5, 13.7Hz);
3.48 (1H, doublet of doublets, J = 7.5, 13.7Hz);
5.39 (1H, triplet, J = 7.5Hz);
6.32 (2H, singlet);
6.9-7.0 (2H, multiplet);
7.1-7.5 (12H, multiplet);
8.09 (1H, doublet, J = 7.8Hz);
8.15 (1H, doublet, J = 8.2Hz).

EXAMPLE 18

tert-Butyl 2-[9-(4-chlorobenzyl)-1-methylthio- carbazol-2-yl]-3-(4-chlorophenyl)propionate

Following a procedure and using relative proportions of starting materials similar to those described in Example 16, but using 4-chlorobenzyl chloride as starting material, the title compound was obtained as an oil in a yield of 95%.

EXAMPLE 19

2-[9-(4-Chlorobenzyl)-1-methylthiocarbazol-2-yl]- 3-(4-chlorophenyl)propionic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl 2-(9-(4-chlorobenzyl)-1-methylthiocarbazol-2-yl)-3-(4-chlorophenyl)propionate, as obtained in Example 18 as starting material, the title compound was obtained in quantitative yield, melting at 104 - 107°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.95 (3H, singlet);
3.02 (1H, doublet of doublets, $J = 7.5, 13.8\text{Hz}$);
3.43 (1H, doublet of doublets, $J = 7.5, 13.8\text{Hz}$);
5.35 (1H, triplet, $J = 7.5\text{Hz}$);
6.27 (2H, singlet);
6.8-7.5 (12H, multiplet);
8.0-8.2 (2H, multiplet).

EXAMPLE 20

tert-Butyl 2-[9-(4-fluorobenzyl)-1-methylthio-
carbazol-2-yl]-3-(4-fluorophenyl)propionate

Following a procedure and using relative proportions of starting materials similar to those described in Example 16, but using 4-fluorobenzyl bromide as starting material, the title compound was obtained as an oil in a yield of 97%.

EXAMPLE 21

2-[9-(4-Fluorobenzyl)-1-methylthiocarbazol-2-yl]-3-
(4-fluorophenyl)propionic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl 2-[9-(4-fluorobenzyl)-1-methylthiocarbazol-2-yl]-3-(4-fluorophenyl)propionate, as obtained in Example 20, as starting material, the title compound was obtained in quantitative yield, melting at $90 - 94^\circ\text{C}$.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

- 1.93 (3H, singlet);
- 3.03 (1H, doublet of doublets, $J = 7.5, 13.7\text{Hz}$);
- 3.44 (1H, doublet of doublets, $J = 7.5, 13.7\text{Hz}$);
- 5.36 (1H, triplet, $J = 7.5\text{Hz}$);
- 6.25 (2H, singlet);
- 6.7-7.5 (12H, multiplet);
- 8.0-8.2 (2H, multiplet).

EXAMPLE 22

tert-Butyl 2-[9-(4-nitrobenzyl)-1-methylthio-
carbazol-2-yl]-3-(4-nitrophenyl)propionate

Following a procedure and using relative proportions of starting materials similar to those described in Example 16, but using 4-nitrobenzyl bromide as starting material, the title compound was obtained as an oil in a yield of 92%.

EXAMPLE 23

2-[9-(4-Nitrobenzyl)-1-methylthiocarbazol-2-yl]-3-
(4-nitrophenyl)propionic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl 2-[(9-(4-nitrobenzyl)-1-methylthiocarbazol-2-yl)-3-(4-nitrophenyl)propionate, as obtained in Example 22, as starting material, the title compound was obtained in quantitative yield as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.96 (3H, singlet);
3.13 (1H, doublet of doublets, $J = 7.5, 13.7\text{Hz}$);
3.56 (1H, doublet of doublets, $J = 7.5, 13.7\text{Hz}$);
5.37 (1H, triplet, $J = 7.5\text{Hz}$);
6.28 (1H, doublet, $J = 17.8\text{Hz}$);
6.47 (1H, doublet, $J = 17.8\text{Hz}$);
7.12 (2H, doublet, $J = 8.7\text{Hz}$);
7.2-7.5 (6H, multiplet);
8.0-8.2 (6H, multiplet).

EXAMPLE 24

Benzyl 2-[9-benzyl-4-methyl-1-methylthiocarbazol-2-yl]-3-phenylpropionate

A solution of 100 mg of benzyl (9-benzyl-4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 13 a), in 1 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 23 mg of sodium hydride (55% w/w dispersion in mineral oil) in 3 ml of N,N-dimethylformamide. 91 mg of benzyl bromide were then added to the reaction mixture which was then warmed to room temperature and stirred for 1 hour. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate and the organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 3 g of silica gel with a 1 : 2 v/v mixture of hexane and benzene as the eluent, to yield 142 mg of the title compound as an oil.

EXAMPLE 252-(9-Benzyl-4-methyl-1-methylthiocarbazol-2-yl)-3-phenyl-propionic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using benzyl 2-(9-benzyl-4-methyl-1-methylthiocarbazol-2-yl)-3-phenylpropionate, as obtained in Example 24, as starting material, the title compound was obtained in a yield of 91%, melting at 199 - 200°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

- 1.85 (3H, singlet);
- 2.92 (3H, singlet);
- 3.03 (1H, doublet of doublets, $J = 7.4, 13.7\text{Hz}$);
- 3.46 (1H, doublet of doublets, $J = 7.4, 13.7\text{Hz}$);
- 5.38 (1H, triplet, $J = 7.4\text{Hz}$);
- 6.36 (2H, singlet);
- 6.99 (2H, doublet, $J = 7.9\text{Hz}$);
- 7.1-7.5 (12H, multiplet);
- 8.20 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 261-Methylcarbazole-2-carboxylic acid

4 ml of ethanol and 4 ml of a 2N aqueous solution of potassium hydroxide were added to 100 mg of ethyl 1-methylcarbazole-2-carboxylate [obtained according to the procedures described in C.J. Moody and K.F. Rahimtoola, J. Chem. Soc. Parkin. Trans. I, 673 (1990)]. The reaction mixture was stirred for 2 hours at room temperature, and then acidified by the addition of a 1N aqueous solution of hydrochloric acid, after

which it was concentrated by evaporation under reduced pressure. Ethyl acetate was added to the residue. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was recrystallized from ethyl acetate and hexane, to yield 81 mg of the title compound, melting at $>240^{\circ}\text{C}$.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.89 (3H, singlet);
7.24 (1H, triplet, $J = 8.0\text{Hz}$);
7.45 (1H, triplet, $J = 8.0\text{Hz}$);
7.52 (1H, doublet, $J = 8.0\text{Hz}$);
7.90 (1H, doublet, $J = 8.4\text{Hz}$);
7.94 (1H, doublet, $J = 8.4\text{Hz}$);
8.09 (1H, doublet, $J = 8.0\text{Hz}$);
8.89 (1H, broad singlet).

EXAMPLE 27

1-Methylcarbazole-3-carboxylic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl 1-methylcarbazole-3-carboxylate as starting material, the title compound was obtained in a yield of 92%, melting at $>240^{\circ}\text{C}$.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.61 (3H, singlet);
7.26 (1H, triplet, $J = 7.8\text{Hz}$);
7.43 (1H, triplet, $J = 7.8\text{Hz}$);

7.51 (1H, doublet, $J = 7.8\text{Hz}$);
7.98 (1H, singlet);
8.10 (1H, doublet, $J = 7.8\text{Hz}$);
8.71 (1H, singlet);
9.20 (1H, broad singlet).

EXAMPLE 28

Ethyl 9-benzyl-1-methylcarbazole-2-carboxylate

A solution of 29 mg of ethyl 1-methylcarbazole-2-carboxylate in 1 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 10 mg of sodium hydride (55% w/w dispersion in mineral oil) in 2 ml of N,N-dimethylformamide. 29 mg of benzyl bromide was then added to the reaction mixture, which was then stirred for 1 hour, with ice-cooling. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate and the organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 1 g of silica gel with a 9 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 38 mg of the title compound, melting at 79 - 80°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.40 (3H, triplet, $J = 7.1\text{Hz}$);
2.80 (3H, singlet);
4.38 (2H, quartet, $J = 7.1\text{Hz}$);
5.79 (2H, singlet);
7.07 (2H, doublet, $J = 6.5\text{Hz}$);
7.2-7.5 (6H, multiplet);
7.66 (1H, doublet, $J = 8.2\text{Hz}$);

7.99 (1H, doublet, J = 8.2Hz);
8.12 (1H, doublet, J = 8.0Hz).

EXAMPLE 29

9-Benzyl-1-methylcarbazole-2-carboxylic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl 9-benzyl-1-methylcarbazole-2-carboxylate, as obtained in Example 28, as starting material, the title compound was obtained in a yield of 94%, melting at 215 - 216°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),
δ ppm:

2.85 (3H, singlet);
5.80 (2H, singlet);
7.0-7.1 (2H, multiplet);
7.2-7.4 (5H, multiplet);
7.44 (1H, triplet, J = 7.5Hz);
7.76 (1H, doublet, J = 8.1Hz);
7.99 (1H, doublet, J = 8.1Hz);
8.12 (1H, doublet, J = 7.5Hz).

EXAMPLE 30

Ethyl 9-benzyl-1-methylcarbazole-3-carboxylate

Following a procedure and using relative proportions of starting materials similar to those described in Example 28, but using ethyl 1-methylcarbazole-3-carboxylate as starting material, the title compound was obtained in a yield of 96%, melting at 118 - 119°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.44 (3H, triplet, $J = 7.1\text{Hz}$);
2.64 (3H, singlet);
4.43 (2H, quartet, $J = 7.1\text{Hz}$);
5.74 (2H, singlet);
6.9-7.0 (2H, multiplet);
7.2-7.5 (6H, multiplet);
7.87 (1H, singlet);
8.16 (1H, doublet, $J = 8.2\text{Hz}$);
8.72 (1H, singlet).

EXAMPLE 31

9-Benzyl-1-methylcarbazole-3-carboxylic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl 9-benzyl-1-methylcarbazole-3-carboxylate, as obtained in Example 30, as starting material, the title compound was obtained in a yield of 92%, melting at $>240^\circ\text{C}$.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.70 (3H, singlet);
5.83 (2H, singlet);
7.0-7.1 (2H, multiplet);
7.2-7.4 (5H, multiplet);
7.46 (1H, triplet, $J = 7.6\text{Hz}$);
7.93 (1H, singlet);
8.18 (1H, doublet, $J = 7.6\text{Hz}$);
8.79 (1H, singlet).

EXAMPLE 32Methyl (1-methylcarbazol-3-yl)acetate

73 mg of oxalyl chloride was added, with ice-cooling, to a solution of 92 mg of 1-methylcarbazole-3-carboxylic acid, as obtained in Example 27, in 5 ml of methylene chloride. One drop of N,N-dimethylformamide was then added to the reaction mixture, which was next warmed to room temperature, stirred for 2 hours, and then concentrated by evaporation under reduced pressure. 10 ml of diethyl ether and an excess of a solution of diazomethane in diethyl ether were added to the residue thus obtained, and the reaction mixture was stirred for one night at room temperature. Acetic acid and then a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 2 g of silica gel with a 1 : 1 v/v mixture of hexane and ethyl acetate as the eluent. Subsequently, 6 mg of silver oxide was added to a solution of the eluted residue in 5 ml of methanol. The reaction mixture was refluxed for 5 hours, filtered to remove inorganic materials, and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 2 g of silica gel with a 2 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 90 mg of the title compound as an oil.

EXAMPLE 33(1-Methylcarbazol-3-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using methyl (1-methylcarbazol-3-yl)-acetate, as obtained in Example 32, as starting material, the title compound was obtained in a yield of 93%, melting at 177 - 179°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

- 2.56 (3H, singlet);
- 3.81 (2H, singlet);
- 7.1-7.5 (5H, multiplet);
- 7.85 (1H, singlet);
- 7.97 (1H, broad singlet);
- 8.04 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 349-Benzyl-1-methylcarbazole-2-carbaldehyde

1.6 ml of a 1.5 M solution of diisobutylaluminum hydride in hexane was added at -78°C to a solution of 213 mg of ethyl 9-benzyl-1-methylcarbazole-2-carboxylate, as obtained in Example 28, in 5 ml of methylene chloride. The reaction mixture was stirred for 1 hour at this temperature, warmed to room temperature, and then stirred for a further 1 hour at room temperature. After this time, 0.1 ml of water, 0.1 ml of a 1N aqueous solution of sodium hydroxide and 0.3 ml of water were added successively to the reaction mixture. Precipitated crystals were filtered off and the filtrate was then concentrated by evaporation under reduced

pressure. 187 mg of pyridinium dichromate and molecular sieve 4A, followed by 2 ml of methylene chloride, were added to 100 mg of the thus obtained residue. The resulting mixture was stirred for two hours at room temperature, filtered using Florisil (trade mark), and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 2 g of silica gel with a 5 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 94 mg of the title compound as an amorphous solid.

EXAMPLE 35

Ethyl 3-(9-benzyl-1-methylcarbazol-2-yl)-3-propenoate

90 mg of ethyl diethylphosphonoacetate was added, with ice-cooling, to a suspension of 18 mg of sodium hydride (55% w/w dispersion in mineral oil) in 2 ml of tetrahydrofuran, and the reaction mixture was stirred for 15 minutes. A solution of 83 mg of 9-benzyl-1-methylcarbazole-2-carbaldehyde, as obtained in Example 34, in tetrahydrofuran was then added to the reaction mixture, which was then stirred for 15 minutes. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 2 g of silica gel with a 5 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 97 mg of the title compound as an amorphous solid.

EXAMPLE 36Ethyl 3-(9-benzyl-1-methylcarbazol-2-yl)propionate

10 mg of 10% w/w palladium on charcoal was added to a solution of 89 mg of ethyl 3-(9-benzyl-1-methylcarbazol-2-yl)-3-propenoate, as obtained in Example 35, in 1 ml each of methanol and of tetrahydrofuran. The reaction mixture was stirred for 1 hour under a stream of hydrogen gas at room temperature, filtered to remove the catalyst, and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 2 g of silica gel with a 5 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 85 mg of the title compound, melting at 114 - 115°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.24 (3H, triplet, $J = 7.2\text{Hz}$);
2.57 (3H, singlet);
2.59 (2H, triplet, $J = 8.2\text{Hz}$);
3.11 (2H, triplet, $J = 8.2\text{Hz}$);
4.13 (2H, quartet, $J = 7.2\text{Hz}$);
5.76 (2H, singlet);
7.0-7.4 (8H, multiplet);
7.37 (1H, triplet, $J = 7.0\text{Hz}$);
7.91 (1H, doublet, $J = 7.9\text{Hz}$);
8.06 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 373-(9-Benzyl-1-methylcarbazol-2-yl)propionic acid

Following a procedure and using relative proportions of starting materials similar to those described in

Example 26, but using ethyl 3-(9-benzyl-1-methylcarbazol-2-yl)propionate, as obtained in Example 36, as starting material, the title compound was obtained in a yield of 97%, melting at 160 - 162°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

- 2.57 (3H, singlet);
- 2.66 (2H, triplet, $J = 8.1\text{Hz}$);
- 3.13 (2H, triplet, $J = 8.1\text{Hz}$);
- 5.77 (2H, singlet);
- 7.0-7.4 (9H, multiplet);
- 7.92 (1H, doublet, $J = 7.9\text{Hz}$);
- 8.07 (1H, doublet, $J = 7.7\text{Hz}$).

EXAMPLE 38

(Carbazol-2-yl)thioacetomorpholide

96 mg of morpholine and 18 mg of sulfur powder were added to 157 mg of 2-acetylcarbazole [obtained according to the procedures described by S.G.P. Plant and S.B.C. Williams, J. Chem. Soc., 1142 (1934)]. The reaction mixture was stirred for 5 hours at 80°C, and then acidified by the addition of a 0.5N aqueous solution of hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 5 g of silica gel with a 2 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 195 mg of the title compound as an amorphous solid.

EXAMPLE 39(Carbazol-2-yl)acetic acid

1 ml of a 4N aqueous solution of potassium hydroxide was added to a solution of 100 mg of (carbazol-2-yl)-thioacetomorpholide, as obtained in Example 38, in 2 ml of ethanol. The reaction mixture was refluxed for 10 hours, after which time it was acidified by the addition of a 1N aqueous solution of hydrochloric acid and was then concentrated by evaporation under reduced pressure. Ethyl acetate was added to the residue. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was recrystallized from ethyl acetate and hexane, to yield 68 mg of the title compound, melting at 150 -152°C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide, 270MHz), δ ppm:

3.76 (2H, singlet);
7.1-7.5 (5H, multiplet);
7.99 (1H, doublet, J = 8.2Hz);
8.02 (1H, doublet, J = 9.2Hz);
9.21 (1H, broad singlet).

EXAMPLE 402-Acetyl-9-benzylcarbazole

Following a procedure and using relative proportions of starting materials similar to those described in Example 28, but using 2-acetylcarbazole as starting material, the title compound was obtained in a yield of

95% as an amorphous solid.

EXAMPLE 41

(9-Benzylcarbazol-2-yl)acetomorpholide

Following a procedure and using relative proportions of starting materials similar to those described in Example 38, but using 2-acetyl-9-benzylcarbazole, as obtained in Example 40 as starting material, the title compound was obtained in a yield of 88% as an amorphous solid.

EXAMPLE 42

(9-Benzylcarbazol-2-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using (9-benzylcarbazol-2-yl)-acetomorpholide, as obtained in Example 41, as starting material, the title compound was obtained in a yield of 86%, melting at 149 - 150°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 3.80 (2H, singlet);
- 5.50 (2H, singlet);
- 7.1-7.5 (10H, multiplet);
- 8.07 (1H, doublet, $J = 7.6\text{Hz}$);
- 8.10 (1H, doublet, $J = 6.6\text{Hz}$).

EXAMPLE 43tert-Butyl (1-methylthiocarbazol-2-yloxy)acetate

135 mg of powdered potassium carbonate was added to a solution of 112 mg of 2-hydroxy-1-methylthiocarbazole, as obtained in Example 2, in 4 ml of acetone. 956 mg of tert-butyl bromoacetate was added to the reaction mixture which was then stirred for 2 hours at room temperature. After this time, the reaction mixture was poured into ice water, and concentrated by evaporation under reduced pressure. The aqueous layer was extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 3 g of silica gel with a 9 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 140 mg of the title compound as an oil.

EXAMPLE 44(1-Methylthiocarbazol-2-yloxy)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl (1-methylthiocarbazol-2-yloxy)acetate, as obtained in Example 43, as starting material, the title compound was obtained in quantitative yield, melting at 179 - 180°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.50 (3H, singlet);

4.82 (2H, singlet);

6.79 (1H, doublet, J = 8.6Hz);
7.20 (1H, triplet, J = 7.9Hz);
7.37 (1H, triplet, J = 7.9Hz);
7.47 (1H, doublet, J = 7.9Hz);
7.92 (1H, doublet, J = 8.6Hz);
7.96 (1H, doublet, J = 7.9Hz);
8.89 (1H, broad singlet).

EXAMPLE 45

tert-Butyl (9-benzyl-1-methylthiocarbazol-2-yloxy)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 28, but using tert-butyl (1-methylthiocarbazol-2-yloxy)acetate, as obtained in Example 43, as starting material, the title compound was obtained as an oil in a yield of 94%.

EXAMPLE 46

(9-Benzyl-1-methylthiocarbazol-2-yloxy)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl (9-benzyl-1-methylthiocarbazol-2-yloxy)acetate, as obtained in Example 45, as starting material, the title compound was obtained in quantitative yield, melting at 188 - 189°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),
δ ppm:

2.04 (3H, singlet);
4.85 (2H, singlet);
6.25 (2H, singlet);

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6.89 (1H, doublet, $J = 8.2\text{Hz}$);
7.01 (2H, doublet, $J = 6.7\text{Hz}$);
7.1-7.5 (6H, multiplet);
8.05 (1H, doublet, $J = 7.9\text{Hz}$);
8.10 (1H, doublet, $J = 8.4\text{Hz}$).

EXAMPLE 47(2-Hydroxy-1-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl 2-hydroxy-1-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)acetate, as obtained in Example 2, as starting material, the title compound was obtained in a yield of 98%, melting at 156 - 157°C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide, 270MHz), δ ppm:

2.34 (1H, doubled doublet of doublets,
 $J = 5.2, 8.3, 13.5\text{Hz}$);
2.55 (1H, triplet of doublets, $J = 5.2, 13.5\text{Hz}$);
2.72 (2H, singlet);
3.03 (1H, doubled doublet of doublets,
 $J = 5.2, 8.3, 17.3\text{Hz}$);
3.20 (1H, triplet of doublets, $J = 5.2, 17.3\text{Hz}$);
7.10 (1H, triplet, $J = 7.8\text{Hz}$);
7.32 (1H, triplet, $J = 7.8\text{Hz}$);
7.46 (1H, doublet, $J = 7.8\text{Hz}$);
7.62 (1H, doublet, $J = 7.8\text{Hz}$);
11.1 (1H, broad singlet).

EXAMPLE 48Ethyl 1,2,3,4-tetrahydrocarbazole-3-carboxylate

A solution of 1.08 g of phenylhydrazine and 1.84 g of ethyl 4-oxocyclohexanecarboxylate in 25 ml of acetic acid was refluxed for 30 minutes and then poured into ice water. The aqueous layer was extracted with ethyl acetate. The organic extract was washed thoroughly with a saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous magnesium sulfate, and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 50 g of silica gel with a 4 : 1 v/v mixture of hexane and ethyl acetate as the eluent and then recrystallized from ethyl acetate and hexane, to yield 2.28 g of the title compound, melting at 95 - 96°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.30 (3H, triplet, $J = 7.1\text{Hz}$);
- 1.9-2.1 (1H, multiplet);
- 2.2-2.4 (1H, multiplet);
- 2.7-3.0 (4H, multiplet);
- 3.08 (1H, doublet of doublets, $J = 5.1, 15.1\text{Hz}$);
- 4.20 (2H, quartet, $J = 7.1\text{Hz}$);
- 7.08 (1H, triplet, $J = 7.1\text{Hz}$);
- 7.13 (1H, triplet, $J = 7.1\text{Hz}$);
- 7.27 (1H, doublet, $J = 7.1\text{Hz}$);
- 7.47 (1H, doublet, $J = 7.1\text{Hz}$);
- 7.72 (1H, broad singlet).

EXAMPLE 491,2,3,4-Tetrahydrocarbazole-3-carboxylic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl 1,2,3,4-tetrahydrocarbazole-3-carboxylate, as obtained in Example 48, as starting material, the title compound was obtained in a yield of 95%, melting at 198 - 199°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.0-2.2 (1H, multiplet);
2.2-2.4 (1H, multiplet);
2.7-3.2 (5H, multiplet);
7.09 (1H, triplet, $J = 6.8\text{Hz}$);
7.14 (1H, triplet, $J = 6.8\text{Hz}$);
7.29 (1H, doublet, $J = 6.8\text{Hz}$);
7.48 (1H, doublet, $J = 6.8\text{Hz}$);
7.73 (1H, broad singlet).

EXAMPLE 50Benzyl 1,2,3,4-tetrahydrocarbazole-3-carboxylate

5.53 g of powdered potassium carbonate was added to a solution of 4.34 g of 1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, as obtained in Example 49, in 100 ml of N,N-dimethylformamide. 3.76 g of benzyl bromide were added to the reaction mixture, which was then stirred for 1.5 hours at room temperature, after which the mixture was neutralized by the addition of a 0.5N aqueous solution of hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous

magnesium sulfate, and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 150 g of silica gel with a 4 : 1 v/v mixture of hexane and ethyl acetate as the eluent, and recrystallized from ethyl acetate and hexane, to yield 6.04 g of the title compound, melting at 104 - 105°C.

EXAMPLE 51

Benzyl 9-benzoyl-1,2,3,4-tetrahydrocarbazole-3-carboxylate

A solution of 291 mg of benzyl 1,2,3,4-tetrahydrocarbazole-3-carboxylate, as obtained in Example 50, in 2 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 87 mg of sodium hydride (55% w/w dispersion in mineral oil) in 4 ml of N,N-dimethylformamide. 0.12 ml of benzoyl chloride was added to the reaction mixture which was then stirred for 1 hour. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 10 g of silica gel with a 5 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 384 mg of the title compound as an oil.

EXAMPLE 529-Benzoyl-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid

20 mg of 10% w/w palladium on charcoal was added to a solution of 100 mg of benzyl 9-benzoyl-1,2,3,4-tetrahydrocarbazole-3-carboxylate, as obtained in Example 51, in 5 ml each of methanol and of tetrahydrofuran. The reaction mixture was stirred for 3 hours under a stream of hydrogen gas at room temperature, filtered to remove the catalyst, and concentrated by evaporation under reduced pressure. The resulting residue was recrystallized from ethyl acetate and hexane, to yield 75 mg of the title compound, melting at 189 - 190°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.9-2.0 (1H, multiplet);
2.2-2.4 (1H, multiplet);
2.8-3.2 (5H, multiplet);
7.07 (2H, doublet, $J = 3.8\text{Hz}$);
7.20 (1H, triplet of doublets, $J = 4.0, 7.9\text{Hz}$);
7.4-7.8 (6H, multiplet).

EXAMPLE 53Benzyl 9-i-butyryl-1,2,3,4-tetrahydrocarbazole-3-carboxylate

Following a procedure and using relative proportions of starting materials similar to those described in Example 51, but using i-butyryl chloride as starting material, the title compound was obtained as an oil in a yield of 83%.

EXAMPLE 549-i-Butyryl-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 52, but using benzyl 9-i-butyryl-1,2,3,4-tetrahydrocarbazole-3-carboxylate, as obtained in Example 53, as starting material, the title compound was obtained in a yield of 98% as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.34 (3H, doublet, $J = 6.6\text{Hz}$);
- 1.36 (3H, doublet, $J = 6.6\text{Hz}$);
- 1.9-2.1 (1H, multiplet);
- 2.3-2.4 (1H, multiplet);
- 2.8-3.3 (5H, multiplet);
- 3.50 (1H, septet, $J = 6.6\text{Hz}$);
- 7.2-7.4 (2H, multiplet);
- 7.44 (1H, doublet of doublets, $J = 1.8, 7.2\text{Hz}$);
- 7.88 (1H, doublet of doublets, $J = 2.1, 6.8\text{Hz}$).

EXAMPLE 55Ethyl 9-benzyl-1,2,3,4-tetrahydrocarbazole-3-carboxylate

Following a procedure and using relative proportions of starting materials similar to those described in Example 48, but using benzylphenylhydrazine as starting material, the title compound was obtained as an oil in a yield of 89%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

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1.28 (3H, triplet, $J = 7.1\text{Hz}$);
1.9-2.1 (1H, multiplet);
2.2-2.4 (1H, multiplet);
2.6-3.0 (4H, multiplet);
3.12 (1H, doublet of doublets, $J = 5.3, 15.3\text{Hz}$);
4.19 (2H, quartet, $J = 7.1\text{Hz}$);
5.20 (1H, doublet, $J = 17.0\text{Hz}$);
5.27 (1H, doublet, $J = 17.0\text{Hz}$);
6.9-7.0 (2H, multiplet);
7.0-7.4 (6H, multiplet);
7.5-7.6 (1H, multiplet).

EXAMPLE 56

9-Benzyl-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl 9-benzyl-1,2,3,4-tetrahydrocarbazole-3-carboxylate, as obtained in Example 55, as starting material, the title compound was obtained in a yield of 93%, melting at $195 - 196^{\circ}\text{C}$.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.9-2.2 (1H, multiplet);
2.3-2.4 (1H, multiplet);
2.6-3.1 (4H, multiplet);
3.17 (1H, doublet of doublets, $J = 5.1, 10.1\text{Hz}$);
5.22 (1H, doublet, $J = 16.9\text{Hz}$);
5.29 (1H, doublet, $J = 16.9\text{Hz}$);
6.9-7.0 (2H, multiplet);
7.0-7.3 (6H, multiplet);
7.52 (1H, doublet of doublets, $J = 3.1, 5.8\text{Hz}$).

EXAMPLE 57Ethyl 4-oxocyclohexylideneacetate ethylene acetal

Following a procedure and using relative proportions of starting materials similar to those described in Example 35, but using cyclohexane-1,4-dione monoethylene acetal as starting material, the title compound was obtained in a yield of 87% as an oil.

EXAMPLE 58Ethyl 4-oxocyclohexylacetate ethylene acetal

Following a procedure and using relative proportions of starting materials similar to those described in Example 36, but using ethyl 4-oxocyclohexylideneacetate ethylene acetal, as obtained in Example 57, as starting material, the title compound was obtained as an oil in a yield of 95%.

EXAMPLE 59Ethyl 4-oxocyclohexylacetate

50 ml of a 1N aqueous solution of hydrochloric acid was added to a solution of 5.0 g of ethyl 4-oxocyclohexylacetate ethylene acetal, as obtained in Example 58, in 50 ml of acetone. The reaction mixture was stirred for 10 minutes at room temperature, neutralized by the addition of a saturated aqueous solution of sodium hydrogencarbonate, and then concentrated by evaporation under reduced pressure. The resulting residue was extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium

chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 100 g of silica gel with a 4 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 3.9 g of the title compound as an oil.

EXAMPLE 60

Ethyl (1,2,3,4-tetrahydrocarbazol-3-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 48, but using ethyl 4-oxocyclohexylacetate, as obtained in Example 59, as starting material, the title compound was obtained in a yield of 90%, melting at 122 - 123°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.29 (3H, triplet, $J = 7.1\text{Hz}$);
1.6-1.8 (1H, multiplet);
2.0-2.2 (1H, multiplet);
2.3-2.5 (4H, multiplet);
2.7-3.0 (3H, multiplet);
4.18 (2H, quartet, $J = 7.1\text{Hz}$);
7.07 (1H, triplet, $J = 7.0\text{Hz}$);
7.12 (1H, triplet, $J = 7.0\text{Hz}$);
7.27 (1H, doublet, $J = 7.0\text{Hz}$);
7.44 (1H, doublet, $J = 7.0\text{Hz}$);
7.70 (1H, broad singlet).

EXAMPLE 61(1,2,3,4-Tetrahydrocarbazol-3-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl (1,2,3,4-tetrahydrocarbazol-3-yl)acetate, as obtained in Example 60, as starting material, the title compound was obtained in a yield of 95%, melting at 209 - 210°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.6-1.8 (1H, multiplet);
2.0-2.3 (1H, multiplet);
2.3-3.0 (7H, multiplet);
7.01 (1H, triplet, $J = 7.5\text{Hz}$);
7.07 (1H, triplet, $J = 7.5\text{Hz}$);
7.29 (1H, doublet, $J = 7.5\text{Hz}$);
7.41 (1H, doublet, $J = 7.5\text{Hz}$);
8.98 (1H, broad singlet).

EXAMPLE 62Ethyl (9-benzyl-1,2,3,4-tetrahydrocarbazol-3-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Examples 55 and 56, but using ethyl 4-oxocyclohexylacetate, as obtained in Example 59, as starting material, the title compound was obtained as an oil in a yield of 91%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.28 (3H, triplet, $J = 7.1\text{Hz}$);

1.5-1.7 (1H, multiplet);
2.0-2.1 (1H, multiplet);
2.3-2.5 (4H, multiplet);
2.6-2.7 (2H, multiplet);
2.9-3.0 (1H, multiplet);
4.17 (2H, quartet, $J = 7.1\text{Hz}$);
5.21 (1H, doublet, $J = 17.7\text{Hz}$);
5.28 (1H, doublet, $J = 17.7\text{Hz}$);
6.9-7.3 (8H, multiplet);
7.49 (1H, doublet, $J = 6.5\text{Hz}$).

EXAMPLE 63

(9-Benzyl-1,2,3,4-tetrahydrocarbazol-3-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl (9-benzyl-1,2,3,4-tetrahydrocarbazol-3-yl)acetate, as obtained in Example 61, as starting material, the title compound was obtained in a yield of 97%, melting at 156 - 158°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.6-1.8 (1H, multiplet);
2.0-2.1 (1H, multiplet);
2.3-2.8 (6H, multiplet); -
3.01 (1H, doublet of doublets, $J = 4.1, 14.9\text{Hz}$);
5.20 (1H, doublet, $J = 17.9\text{Hz}$);
5.27 (1H, doublet, $J = 17.9\text{Hz}$);
6.9-7.3 (8H, multiplet);
7.50 (1H, doublet, $J = 6.3\text{Hz}$).

EXAMPLE 64Allyl 2-(indol-6-yl)acetate

750 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were added to a solution of 450 mg of 2-(indol-6-yl)acetic acid [synthesized according to the procedures described in Chem. Pharm. Bull., 20, 2163 (1972)], 0.27 ml of allyl alcohol and 480 mg of 4-dimethylaminopyridine in 20 ml of methylene chloride, at room temperature, and the resulting mixture was stirred overnight. After completion of the reaction, the reaction mixture was acidified by the addition of a 3% aqueous solution of hydrochloric acid, followed by extraction with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate, and then the solvent was removed by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 10 g of silica gel with a 4 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 480 mg of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

8.10 (1H, broad singlet);
7.58 (1H, doublet, $J = 8.0\text{Hz}$);
7.34 (1H, singlet);
7.18 (1H, multiplet);
7.05 (1H, doublet, $J = 8.0\text{Hz}$);
6.52 (1H, multiplet);
5.80-6.00 (1H, multiplet);
5.15 - 5.35 (2H, multiplet);
4.55 - 4.65 (2H, multiplet);
3.75 (2H, singlet).

EXAMPLE 65

Allyl 2-benzyl-2-(1-benzylindol-6-yl)acetate
and
Allyl 2-(1-benzylindol-6-yl)acetate

A solution of 100 mg of allyl 2-(indol-6-yl)acetate, as obtained in Example 64, in 1 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 20 mg of sodium hydride (55% w/w dispersion in mineral oil) in 1 ml of N,N-dimethylformamide, and the reaction mixture was stirred at this temperature for 15 minutes. 0.06 ml of benzyl bromide was added to the reaction mixture, with ice-cooling, and the resulting mixture was stirred for a further 30 minutes. After completion of the reaction, water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate, and then the solvent was removed by evaporation under reduced pressure. The residue was purified over column chromatography using 10 g of silica gel with, successively, a 5% v/v solution of ethyl acetate in hexane, and a 10% solution of ethyl acetate in hexane.

44 mg of allyl 2-benzyl-2-(1-benzylindol-6-yl)-acetate were obtained from the first fraction (5% eluent), and

70 mg of allyl 2-(1-benzylindol-6-yl)acetate were obtained from the second fraction (10% eluent).

The Nuclear Magnetic Resonance Spectrum [(CDCl₃, 270MHz), δ ppm] results for each of the above compounds are as follows:

Allyl 2-benzyl-2-(1-benzylindol-6-yl)acetate

7.61 (1H, doublet, J = 8.2Hz);

7.05 - 7.40 (13H, multiplet);
6.54 (1H, doublet, $J = 3.0\text{Hz}$);
5.65 - 5.85 (1H, multiplet);
5.33 (2H, singlet);
5.05 - 5.20 (2H, multiplet);
4.50 - 4.60 (2H, multiplet);
3.99 (1H, doublet of doublets, $J = 8.8, 6.6\text{Hz}$);
3.46 (1H, doublet of doublets, $J = 13.6, 8.8\text{Hz}$);
3.09 (1H, doublet of doublets, $J = 13.6, 6.6\text{Hz}$).

Allyl 2-(1-benzylindol-6-yl)acetate

7.59 (1H, doublet, $J = 8.2\text{Hz}$);
7.00 - 7.30 (8H, multiplet);
6.51 (1H, doublet, $J = 3.4\text{Hz}$);
5.75 - 5.95 (1H, multiplet);
5.29 (2H, singlet);
5.10 - 5.30 (2H, multiplet);
4.50 - 4.60 (2H, multiplet);
3.71 (2H, singlet).

EXAMPLE 66

2-Benzyl-2-(1-benzylindol-6-yl)acetic acid

6 mg of tetrakis(triphenylphosphine) palladium, 7 mg of triphenylphosphine and 65 mg of sodium 2-ethylhexanoate were added to a solution of 104 mg of allyl 2-benzyl-2-(1-benzylindol-6-yl)acetate, as obtained in Example 65, in 5 ml of methylene chloride, and the resulting mixture was stirred at room temperature overnight. After completion of the reaction, the reaction mixture was acidified by the addition of a 3% aqueous solution of hydrochloric acid, followed by extraction with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate, and

then the solvent was removed by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 5 g of silica gel with a 1 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 61 mg of the title compound as a solid material, melting at 148 - 150°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

7.58 (1H, doublet, $J = 8.0\text{Hz}$);
7.00 - 7.30 (13H, multiplet);
6.50 (1H, doublet, $J = 8.0\text{Hz}$);
5.28 (2H, singlet);
3.93 (1H, triplet, $J = 8.0\text{Hz}$);
3.42 (1H, doublet of doublets, $J = 13.8, 8.0\text{Hz}$);
3.05 (1H, doublet of doublets, $J = 13.8, 8.0\text{Hz}$).

EXAMPLE 67

2-(1-Benzylindol-6-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 66, but using 16 mg of allyl 2-(1-benzylindol-6-yl)acetate, as obtained in Example 65, as starting material, 6 mg of the title compound was obtained as a solid material, melting at 109 - 111°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

7.60 (1H, doublet, $J = 8.0\text{Hz}$);
7.00 - 7.35 (8H, multiplet);
6.51 (1H, doublet, $J = 4.0\text{Hz}$);
5.30 (2H, singlet);
3.72 (2H, singlet).

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EXAMPLE 68Allyl 2-(1-benzoylindol-6-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 65, but using 100 mg of allyl 2-(indol-6-yl)-acetate, as obtained in Example 64, and 0.05 ml of benzoyl chloride as starting materials, 65 mg of the title compound was obtained as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

8.41 (1H, singlet);
7.20 - 7.80 (8H, multiplet);
6.61 (1H, doublet, $J = 4.0\text{Hz}$);
5.80 - 6.00 (1H, multiplet);
5.20 - 5.40 (2H, multiplet);
4.55 - 4.70 (2H, multiplet);
3.84 (2H, singlet).

EXAMPLE 692-(1-Benzoylindol-6-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 66, but using 65 mg of allyl 2-(1-benzoylindol-6-yl)acetate, as obtained in Example 68, as starting material, 26 mg of the title compound was obtained as a solid material, melting at 113 - 115°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

8.38 (1H, singlet);
7.20 - 7.80 (8H, multiplet);

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6.59 (1H, doublet, J = 4.0Hz);
3.82 (2H, singlet).

EXAMPLE 70

1-Phenyl-1,2,3,4-tetrahydro- β -carboline

A mixture of 1.0 g (6.24 mmol) of tryptamine and 0.73 g (0.87 mmol) of benzaldehyde in 10 ml of acetic acid was refluxed for 3 hours. After completion of the reaction, the solvent was distilled off, and the residue was made alkaline by the addition of a saturated aqueous solution of sodium hydrogencarbonate, followed by extraction with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, and then the solvent was removed by evaporation under reduced pressure to give 1.82 g of a crude mixture. The resulting residue was subjected to column chromatography using 35 g of silica gel with a 9 : 1 by volume mixture of methylene chloride and methanol as the eluent, to yield 1.43 g (92%) of the title compound. The product was subsequently recrystallized from dichloroethane and hexane to yield 0.72 g of pale yellowish brown crystals.

EXAMPLE 71

Benzyl (1-phenyl-1,2,3,4-tetrahydro- β -carbolin-2-yl)-acetate

147 mg (1.45 mmol) of triethylamine and 277 mg (1.21 mmol) of benzyl bromoacetate were added successively to a solution of 300 mg (1.21 mmol) of 1-phenyl-1,2,3,4-tetrahydro- β -carboline, as obtained in Example 70, in 10 ml of methylene chloride, with

ice-cooling, and the resulting mixture was stirred at room temperature for 3 hours. After this time, 277 mg of benzyl bromoacetate and 183 mg of triethylamine were added to the reaction mixture, and the resulting mixture was allowed to stand for 2 days. At the end of this time, first a saturated aqueous solution of sodium hydrogencarbonate and then water were added successively to the reaction mixture, which was then extracted with ethyl acetate. The resulting extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, and the ethyl acetate was removed by evaporation under reduced pressure to give 0.61 g of a crude mixture. The resulting residue was subjected to column chromatography using 13 g of silica gel with a 9 : 1 by volume mixture of hexane and ethyl acetate as the eluent, to yield 0.49 g of the title compound as yellow crystals in quantitative yield. The product was subsequently recrystallized from ethyl acetate to yield 0.37 g of the title compound as yellow crystals, melting at 130.8 - 132.0°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.80 - 3.30 (4H, multiplet);
3.36 (1H, doublet, $J = 16\text{Hz}$);
3.50 (1H, doublet, $J = 16\text{Hz}$);
5.07 (1H, singlet);
5.12 (1H, doublet, $J = 16\text{Hz}$);
5.18 (1H, doublet, $J = 16\text{Hz}$);
7.05 - 7.57 (15H, multiplet).

EXAMPLE 72(1-Phenyl-1,2,3,4-tetrahydro- β -carbolin-2-yl)acetic acid

A catalytic amount of 10% w/w palladium on charcoal was added under a stream of hydrogen to a solution of 260.2 mg (0.656 mmol) of benzyl (1-phenyl-1,2,3,4-tetrahydro- β -carbolin-2-yl)acetate, as obtained in Example 71, in 2 ml each of methanol and of tetrahydrofuran, and hydrogenation was allowed to proceed for 3 hours. The palladium on charcoal catalyst was removed from the reaction mixture by filtration, and the solvent was removed by evaporation under reduced pressure to give 0.32 g of a crude mixture. The resulting residue was subjected to column chromatography using 5 g of silica gel with a 19 : 1 by volume mixture of methylene chloride and methanol as the eluent, to yield 0.05 g of the title compound as a pale yellow powder, melting at 157 - 164°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.20 - 4.13 (6H, multiplet);
6.11 (1H, singlet);
7.15 - 7.65 (10H, multiplet);
8.07 (1H, singlet).

EXAMPLE 73tert-Butyl [9-(4-methoxybenzyl)-1-methylthio-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using 4-methoxybenzyl bromide as starting

material, the title compound was obtained as an oil in a yield of 98%.

EXAMPLE 74

[9-(4-Methoxybenzyl)-1-methylthiocarbazol-2-yl]acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(4-methoxybenzyl)-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 73, as starting material, the title compound was obtained in quantitative yield as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.01 (3H, singlet);
3.71 (3H, singlet);
4.22 (2H, singlet);
6.28 (2H, singlet);
6.75 (2H, doublet, $J = 8.7\text{Hz}$);
6.96 (2H, doublet, $J = 8.7\text{Hz}$);
7.2-7.5 (4H, multiplet);
8.07 (1H, doublet, $J = 7.6\text{Hz}$);
8.09 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 75

9-Benzyl-1-methylthiocarbazole-2-acetamide

An excess of a solution of diazomethane in diethyl ether was added to a solution of 150mg of 9-benzyl-1-methylthiocarbazol-2-acetic acid, as obtained in Example 5, in 3 ml of diethyl ether. The resulting reaction

mixture was stirred for 10 minutes at room temperature and then glacial acetic acid was added. The reaction mixture was next concentrated by evaporation under reduced pressure. 10 ml of saturated methanolic ammonia was added to a solution of the resulting residue in 5 ml of methanol, and the reaction mixture was stirred for 7 days at room temperature. After this time, the reaction mixture was concentrated by evaporation under reduced pressure and the resulting residue was subjected to column chromatography using 400 mg of silica gel using, as eluent, a 4 : 1 by volume mixture of hexane and ethyl acetate to yield 131 mg of the title compound as an amorphous solid.

EXAMPLE 76

9-Benzyl-1-methylthiocarbazol-2-acetonitrile

32 mg of p-toluene sulfonyl chloride was added to a solution of 20mg of 9-benzyl-1-methylthiocarbazole-2-acetamide, as obtained in Example 75, in 0.6 ml of pyridine at room temperature. The reaction mixture was then heated to 60°C and stirred for 2 hours. The reaction mixture was then cooled to room temperature and water was added. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with a 0.5N aqueous solution of hydrochloric acid, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 50 mg of silica gel using, as eluent, a 4 : 1 by volume mixture of hexane and ethyl acetate to yield 18 mg of the title compound as an oil.

EXAMPLE 775-[(9-Benzyl-1-methylthiocarbazol)-2-ylmethyl]-
1H-tetrazole

64 mg of ammonium chloride and 78 mg of sodium azide were added to a solution of 13 mg of 9-benzyl-1-methylthiocarbazol-2-acetonitrile, as obtained in Example 76, in 3 ml of N,N-dimethylformamide, at room temperature. The reaction mixture was then heated to 130°C and stirred for 1 day. After this time, the reaction mixture was cooled to room temperature and water was added. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 40 mg of silica gel using, as eluent, a 1 : 5 by volume mixture of hexane and ethyl acetate to yield 14 mg of the title compound as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl₃,
270 MHz), δ ppm:

1.91 (3H, singlet);
4.81 (2H, singlet);
6.30 (2H, singlet);
6.9 - 7.1 (2H, multiplet);
7.1 - 7.5 (7H, multiplet);
8.1 - 8.2 (2H, multiplet).

EXAMPLE 782-[4-tert-Butyldiphenylsilyloxy-2-(indol-2-ylthio)-
butyl]-4,4-dimethyl-2-oxazolinea) 2-(4-tert-Butyldiphenylsilyloxy-2-hydroxybutyl)-4,4-
dimethyl-2-oxazoline

5.2 ml of a solution of 1.6 M n-butyllithium in hexane was added dropwise to a solution of 940 mg of 2,4,4-trimethyl-2-oxazoline in 20 ml of tetrahydrofuran with stirring, at -78°C. The resulting mixture was stirred at -78°C for 1 hour. After this time, 2.00 g of 3-tert-butyldiphenylsilyloxy-1-propanal [prepared as described in Can. J. Chem., 71, 695 (1993)] in 10 ml of tetrahydrofuran was added to the reaction mixture whilst stirring, maintaining the temperature at -78°C. Stirring was continued at -78°C for 15 minutes, then the reaction mixture was brought to room temperature and stirred for 30 minutes. At the end of this time, the reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate fraction was washed with water, dried over anhydrous sodium sulfate and the solvent removed by evaporation under reduced pressure. The resulting residue was purified by silica gel column chromatography, using a mixture of 50% v/v ethyl acetate and hexane as the eluent, to afford 2.18 g of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm:

- 1.05 (9H, singlet),
- 1.26 (6H, singlet),
- 1.70-1.80 (2H, multiplet),
- 2.35-2.45 (2H, multiplet),
- 3.75-3.90 (2H, multiplet),
- 3.90 (2H, singlet),
- 4.15-4.20 (1H, multiplet),

4.25 (1H, broad singlet),
7.30-7.70 (10H, multiplet).

b) 2-[4-tert-Butyldiphenylsilyloxy-2-(indol-2-ylthio)-butyl]-4,4-dimethyl-2-oxazoline

960 mg of carbon tetrabromide was added to a mixture of 800 mg of 2-(4-tert-butyldiphenylsilyloxy-2-hydroxy-butyl)-4,4-dimethyl-2-oxazoline [prepared as described in a) above] and 760 mg of triphenylphosphine in 20 ml of dichloromethane, with stirring, at room temperature, and stirring was continued at this temperature for 30 minutes. After this time, the solvent was removed by evaporation under reduced pressure and the residue was dissolved in 10 ml of acetone. The resulting solution was added to a suspension of 280 mg of indoline-2-thione [prepared as described in Chem. Pharm. Bull., 32, 877, (1984)] and 400 mg of potassium carbonate in 20 ml of acetone, and this mixture was stirred at room temperature for 1 hour. At the end of this time, the solvent was removed by evaporation under reduced pressure, and the resulting residue was diluted with water and then extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a mixture of 20% v/v ethyl acetate in hexane as the eluent, to afford 460 mg of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

1.05 (9H, singlet),
1.38 (3H, singlet),
1.42 (3H, singlet),
1.70-1.80 (2H, multiplet),
2.30-2.60 (2H, multiplet),

3.35-3.45 (1H, multiplet),
3.70-3.85 (2H, multiplet),
4.02 (2H, singlet),
6.58 (1H, singlet),
7.05-7.70 (14H, multiplet).

EXAMPLE 79

2-[4-Hydroxy-2-(indol-2-ylthio)butyl]-4,4-dimethyl-2-oxazoline

1 ml of a 1 M solution of tetra-n-butyl ammonium fluoride in tetrahydrofuran was added to a solution of 460 mg of 2-[4-tert-butyl-diphenylsilyloxy-2-(indol-2-ylthio)butyl]-4,4-dimethyl-2-oxazoline [prepared as described in Example 78 b)] in 20 ml of tetrahydrofuran, with stirring, at room temperature, and stirring was continued at this temperature for 30 minutes. After this time, the reaction mixture was diluted with water and then extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the resulting residue was purified by silica gel column chromatography, using a mixture of 60% v/v ethyl acetate in hexane as the eluent, to afford 165 mg of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

1.36 (3H, singlet),
1.40 (3H, singlet),
1.70-1.85 (2H, multiplet),
2.45-2.55 (2H, multiplet),
3.30-3.45 (1H, multiplet),
3.70-4.00 (2H, multiplet),
4.02 (2H, singlet),

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6.67 (1H, singlet),
7.05-7.60 (4H, multiplet).

EXAMPLE 802-(2,3,4,9-Tetrahydrothiopyrano[2,3-b]indol-2-yl)methyl-4,4-dimethyl-2-oxazoline

0.05 ml of methanesulfonyl chloride was added to a mixture of 165 mg of 2-[4-hydroxy-2-(indol-2-ylthio)-butyl]-4,4-dimethyl-2-oxazoline (prepared as described in Example 79) and 0.10 ml of triethylamine in 5 ml of dichloromethane, with stirring and ice-cooling, and stirring was continued for 30 minutes. At the end of this time, the reaction mixture was diluted with water and then extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the resulting residue was dissolved in a mixture of 5 ml of dichloromethane and 5 ml of benzene. 0.26 ml of a solution of 3 M ethylmagnesium bromide in diethyl ether was then added to this mixture, with stirring, at room temperature, and stirring was continued at this temperature for 30 minutes. At the end of this time, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride and then extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a mixture of 30% v/v ethyl acetate in hexane as the eluent, to afford 73 mg of the title compound as a solid.

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Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

1.38 (6H, singlet),
2.05-2.40 (2H, multiplet),
2.68 (2H, doublet, $J = 7.0\text{Hz}$),
2.88 (2H, triplet, $J = 7.0\text{Hz}$),
3.75-3.85 (1H, multiplet),
3.95 (2H, singlet),
7.05-7.40 (4H, multiplet),
7.73 (1H, broad singlet).

EXAMPLE 81

2-(9-Benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)methyl-4,4-dimethyl-2-oxazoline

71 mg of 2-(2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)methyl-4,4-dimethyl-2-oxazoline (prepared as described in Example 80) in 1 ml of dimethylformamide was added to a suspension of 11 mg of sodium hydride (55% w/w dispersion in mineral oil) in 1 ml of dimethylformamide, with stirring and ice-cooling. Stirring was continued at this temperature for 30 minutes and then 0.03 ml of benzyl bromide was added to the reaction mixture, with stirring and ice-cooling. Stirring was continued for a further hour. At the end of this time, the reaction mixture was diluted with water and then extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the resulting residue was purified by silica gel column chromatography, using a mixture of 20% v/v ethyl acetate in hexane as the eluent, to afford 71 mg of the title compound as an oil.

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Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

1.28 (6H, singlet),
2.05-2.40 (2H, multiplet),
2.68 (2H, doublet, $J = 7.0\text{Hz}$),
2.94 (2H, triplet, $J = 7.0\text{Hz}$),
3.75-3.85 (1H, multiplet),
3.93 (2H, singlet),
5.19 (2H, singlet),
7.05-7.45 (9H, multiplet).

EXAMPLE 82

Ethyl 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]-
indol-2-yl)acetate

60 mg of 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano-[2,3-b]indol-2-yl)methyl-4,4-dimethyl-2-oxazoline (prepared as described in Example 81) was dissolved in 5% v/v sulfuric acid in ethanol, and the mixture was refluxed for 6 hours. After this time, the reaction mixture was neutralized by the addition of a saturated aqueous solution of sodium hydrogencarbonate and then extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a mixture of 20% v/v ethyl acetate in hexane as the eluent, to afford 46 mg of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

1.25 (3H, triplet, $J = 7.0\text{ Hz}$),
2.05-2.35 (2H, multiplet),
2.65-2.80 (2H, multiplet),
2.80-2.95 (2H, multiplet),

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3.80-3.90 (1H, multiplet),
4.16 (2H, quartet, J = 7.0 Hz),
5.20 (2H, singlet),
7.05-7.45 (9H, multiplet).

EXAMPLE 83

2-(9-Benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl) acetic acid

0.5 ml of a 3% w/v aqueous solution of potassium hydroxide was added to a mixture of 44 mg of ethyl 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]-indol-2-yl)acetate (prepared as described in Example 82) in 2 ml of ethanol. The reaction mixture was then stirred at room temperature for 2 hours. At the end of this time, the reaction mixture was made acidic by the addition of a 3% w/v aqueous solution of hydrochloric acid and extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the resulting residue was recrystallized from hexane and ethyl acetate to afford 37 mg of the title compound as a solid which melted at 164 - 167°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm:

2.18-2.40 (2H, multiplet),
2.70-2.85 (2H, multiplet),
2.85-3.05 (2H, multiplet),
3.80-3.90 (1H, multiplet),
5.20 (2H, singlet),
7.05-7.50 (9H, multiplet).

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EXAMPLE 845-(9-Benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)methyltetrazole

(a) 0.015 ml of ethyl chloroformate was added to a mixture of 45 mg of 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl) acetic acid (prepared as described in Example 83) and 0.02 ml triethylamine in 2 ml of tetrahydrofuran, with stirring and ice-cooling, and stirring was continued for 15 minutes. After this time, an excess of methanolic ammonia was added to the reaction mixture which was then stirred for a further 15 minutes. At the end of this time, the resulting mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure to afford 21 mg of the amide as a solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

2.05-2.35 (2H, multiplet),
2.55 (2H, doublet, $J = 7.0\text{Hz}$),
2.80-3.00 (2H, multiplet),
3.85-3.95 (1H, multiplet),
5.19 (2H, singlet),
5.42 (1H, broad singlet),
5.67 (1H, broad singlet),
7.05-7.45 (9H, multiplet).

(b) 0.017 ml of trifluoroacetic anhydride was added to a mixture of 20 mg of the compound prepared in (a) and 0.02 ml of pyridine in 1 ml of dichloromethane, with stirring and ice-cooling, and stirring was continued for 30 minutes with ice-cooling. At the end of this time, the reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate

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fraction was then washed with a 3% w/v aqueous solution of hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and then water in that order, before being dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure to afford 20 mg of the nitrile as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

2.20-2.40 (2H, multiplet),
2.75 (2H, doublet, $J = 7.0\text{Hz}$),
2.80-3.05 (2H, multiplet),
3.60-3.70 (1H, multiplet),
5.18 (2H, singlet),
7.05-7.45 (9H, multiplet).

(c) 30 mg of sodium azide and 30 mg of ammonium chloride were added to a mixture of 20 mg of the compound prepared in (b) in 2 ml of dimethylformamide. The reaction mixture was stirred at 130°C for 12 hours. At the end of this time, the reaction mixture was made acidic by the addition of a 3% w/v aqueous solution of hydrochloric acid. The mixture was then extracted with ethyl acetate and the ethyl acetate fraction was washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using ethyl acetate as the eluent, to afford 14 mg of the title compound as a solid which melted at $160 - 165^\circ\text{C}$.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

2.10-2.35 (2H, multiplet),
2.85-3.00 (2H, multiplet),
3.15-3.35 (2H, multiplet),
3.70-3.80 (1H, multiplet),
5.20 (2H, singlet),
7.00-7.45 (10H, multiplet).

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EXAMPLE 85Diphenylmethyl 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano-[2,3-b]indol-2-yl)acetate

An excess of diphenyldiazomethane was added to a mixture of 100 mg of 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)acetic acid (prepared as described in Example 83) in 5 ml of ethyl acetate, with stirring, at room temperature, and stirring was continued at this temperature overnight. At the end of this time, the solvent was removed by evaporation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a mixture of 6% v/v ethyl acetate in hexane as the eluent, to afford 139 mg of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm:

2.00-2.30 (2H, multiplet),
2.70-3.00 (4H, multiplet),
3.80-3.90 (1H, multiplet),
5.15 (2H, singlet),
6.92 (1H, singlet),
7.00-7.50 (19H, multiplet).

EXAMPLE 862-(9-Benzyl-1-oxy-2,3,4,9-tetrahydrothiopyrano[2,3-b]-indol-2-yl)acetic acid

40 mg of m-chloroperbenzoic acid was added to a mixture of 100 mg of diphenylmethyl 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)acetate (prepared as described in Example 85) in 5 ml of dichloromethane, with stirring and ice-cooling, and stirring was continued for 30 minutes. At the end of this time, the

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reaction mixture was diluted with dichloromethane and then washed first with a saturated aqueous solution of sodium hydrogencarbonate and then with water, before drying over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure. 2.5 ml of anisole and 2.5 ml of trifluoroacetic acid were added to 101 mg of the resulting residue, with stirring and ice-cooling, and stirring was continued for 15 minutes. At the end of this time, the reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the resulting residue was purified by silica gel column chromatography, using ethyl acetate as the eluent, to afford 38 mg of the title compound as a powder.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

2.30-2.70 (2H, multiplet),
3.05-3.15 (2H, multiplet),
3.20-3.35 (2H, multiplet),
4.05-4.15 (1H, multiplet),
5.55 (2H, singlet),
7.05-7.60 (9H, multiplet).

EXAMPLE 87

2-(9-Benzyl-1,1-dioxy-2,3,4,9-tetrahydrothiopyrano- [2,3-b]indol-2-yl)acetic acid

40 mg of m-chloroperbenzoic acid was added to a solution of 50 mg of diphenylmethyl 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)acetate (prepared as described in Example 85) in 5 ml of dichloromethane, with stirring and ice-cooling, and stirring was

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continued at room temperature for 1 hour. At the end of this time, the reaction mixture was diluted with dichloromethane and then washed first with a saturated aqueous solution of sodium hydrogencarbonate and then water, before drying over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure. 1 ml of anisole and 1 ml of trifluoroacetic acid were added to 48 mg of the resulting residue, with stirring and ice-cooling, and stirring was continued for 30 minutes. At the end of this time, the reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using ethyl acetate as the eluent, to afford 22 mg of the title compound as a powder.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm:

2.40-2.80 (2H, multiplet),
3.05-3.15 (2H, multiplet),
3.20-3.35 (2H, multiplet),
4.10-4.20 (1H, multiplet),
5.55 (2H, singlet),
7.05-7.60 (9H, multiplet).

EXAMPLE 88

1-Benzyl-4-cyanoindole

Following a procedure and using relative proportions of starting materials similar to those described in Example 65, but using 4-cyanoindole as starting material, the title compound was obtained in a yield of 94%.

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Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:
5.37 (2H, singlet),
6.77 (1H, doublet, $J = 3.4$ Hz),
7.05-7.50 (9H, multiplet).

EXAMPLE 89

4-Acetyl-1-benzylindole

3.3 ml of a 2 M solution of methylmagnesium iodide in diethyl ether was added to a mixture of 1.00 g of 1-benzyl-4-cyanoindole (prepared as described in Example 88) in 50 ml of tetrahydrofuran, with ice-cooling, and the reaction mixture was stirred for 1 hour. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with diethyl ether, and the resulting organic fraction was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was purified by silica gel column chromatography, using 50 g of silica gel and a 4 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 1.00 g of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:
2.57 (3H, singlet),
5.45 (2H, singlet),
7.00-7.50 (10H, multiplet).

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EXAMPLE 90(1-Benzylindol-4-yl)thioacetomorpholide

Following a procedure and using relative proportions of starting materials similar to those described in Example 38, but using 4-acetyl-1-benzylindole (prepared as described in Example 89) as starting material, the title compound was obtained in a yield of 53% as an oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.29 (2H, triplet, $J = 5.2$ Hz),
3.56 (2H, triplet, $J = 5.2$ Hz),
3.76 (2H, triplet, $J = 5.2$ Hz),
4.41 (2H, triplet, $J = 5.2$ Hz),
4.63 (2H, singlet),
5.33 (2H, singlet),
6.60 (1H, doublet, $J = 3.2$ Hz),
7.00-7.35 (9H, multiplet).

EXAMPLE 91(1-Benzylindol-4-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using (1-benzylindol-4-yl)thioacetomorpholide (prepared as described in Example 90) as starting material, the title compound was obtained in a yield of 42%, melting at 138-140°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.93 (2H, singlet),
5.31 (2H, singlet),

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6.59 (1H, doublet, $J = 3.4$ Hz),
7.00-7.35 (9H, multiplet).

EXAMPLE 92

5-(1-Benzylindol-4-yl)methyl-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Example 84, but using 50 mg of (1-benzylindol-4-yl)-acetic acid (prepared as described in Example 91) as starting material, 12 mg of the title compound was obtained as a colorless solid, melting at 201-205°C (with decomposition)

Nuclear Magnetic Resonance Spectrum (CDCl_3 and tetradeuterated methanol, 270MHz), δ ppm:

4.57 (2H, singlet),
5.33 (2H, singlet),
6.47 (1H, doublet, $J = 3.2$ Hz),
7.00-7.55 (9H, multiplet).

EXAMPLE 93

5-(1-Benzylindol-4-yl)-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Example 77, but using 1-benzyl-4-cyanoindole (prepared as described in Example 88) as starting material, the title compound was obtained in a yield of 84%, melting at 224-228°C (with decomposition)

Nuclear Magnetic Resonance Spectrum (CDCl_3 and tetradeuterated methanol, 270MHz), δ ppm:

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5.41 (2H, singlet),
7.00-7.55 (10H, multiplet).

EXAMPLE 94

N-Methanesulfonyl(9-benzylcarbazol-2-yl)acetamide

0.055 ml (0.63 mmol) of oxalyl chloride was added, with ice-cooling, to a mixture of 100 mg (0.32 mmol) of (9-benzylcarbazol-2-yl)acetic acid (prepared as described in Example 42) in 3 ml of methylene chloride, and the whole was stirred for 30 minutes at room temperature. After this time, the solvent was removed by evaporation under reduced pressure. 5 ml of methylene chloride, 0.08 ml (0.99 mmol) of pyridine and 60 mg (0.63 mmol) of methanesulfonamide were added to the residue thus obtained, with ice-cooling. The reaction mixture was then stirred for 12 hours at room temperature. After the reaction had been allowed to go to completion, water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic fraction was then washed with water and dried over anhydrous sodium sulfate, and the solvent was removed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography, using 30 g of silica gel with a 5% v/v solution of methanol in ethyl acetate as eluent, to yield 46 mg of the title compound as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.01 (3H, singlet),
3.83 (2H, singlet),
5.51 (2H, singlet),
7.10-7.95 (12H, multiplet).

EXAMPLE 95N-Methanesulfonyl-(9-benzyl-1-methylcarbazol-2-yl)-
formamide

Following a procedure and using relative proportions of starting materials similar to those described in Example 94, but using (9-benzyl-1-methylcarbazol-2-yl)-carboxylic acid (prepared as described in Example 29) as starting material, the title compound was obtained in a yield of 44%, as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.85 (3H, singlet),

3.03 (3H, singlet),

5.72 (2H, singlet),

7.10-7.65 (10H, multiplet),

8.10 (1H, doublet, $J = 7.0$ Hz).

EXAMPLE 96N-Acetyl-(9-benzyl-1-methylcarbazol-2-yl)methane-
sulfonamide

a) A solution of 400 mg (1.21 mmol) of ethyl (9-benzyl-1-methylcarbazol-2-yl)carboxylate (prepared as described in Example 28) in 10 ml of tetrahydrofuran was added, with ice-cooling, to a suspension of 92 mg (2.42 mmol) of lithium aluminum hydride in 10 ml of tetrahydrofuran, and the resulting mixture was stirred for 30 minutes. After this time, 0.4 ml of 4% w/v aqueous sodium hydroxide was added to the reaction mixture. Precipitated material was filtered off and the filtrate was concentrated by evaporation under reduced pressure to afford 320 mg (1.11 mmol) of the alcohol as an oil.

b) 350 mg (1.68 mmol) of phosphorus pentachloride was added, with ice-cooling, to a solution of 320 mg of the compound obtained in a) and 0.18 ml (2.23 mmol) of pyridine in 15 ml of dichloromethane. The reaction mixture was stirred for 30 minutes. After this time, water was added and the aqueous layer was extracted with diethyl ether. The organic fraction was then washed with water, dried over anhydrous sodium sulfate and concentrated by evaporation under reduced pressure to afford the chloride as an oil.

c) The whole of the compound obtained in b) above and 140 mg (1.11 mmol) of sodium sulfite were added to a mixture of 5 ml of water and 2 ml of dimethyl sulfoxide, and the resulting mixture was heated to 130°C and maintained at this temperature for 14 hours. The solvents were removed by evaporation under reduced pressure, the residue was extracted with methanol, and the filtrate was concentrated to afford the sodium salt of the sulfonic acid as an amorphous solid.

d) 450 mg (2.16 mmol) of phosphorus pentachloride and one drop of POCl_3 were added to the powdered compound obtained in c) above, and the mixture was heated at 70°C for 2 hours. After this time, a large excess of concentrated, aqueous ammonia was added, with ice-cooling, to the reaction mixture. The whole was then stirred overnight at room temperature. The reaction mixture was extracted with methylene chloride, and the organic fraction was washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the residue was purified by silica gel column chromatography, using 30 g of silica gel and a 10% v/v solution of methanol in ethyl acetate as eluent, to yield 98 mg of the sulfonamide as an amorphous solid.

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Nuclear Magnetic Resonance Spectrum (CDCl_3 and tetradeuterated methanol, 270MHz), δ ppm:

2.90 (3H, singlet),
3.87 (2H, singlet),
5.51 (2H, singlet),
7.10-7.85 (11H, multiplet).

e) 0.04 ml (0.56 mmol) of acetyl chloride was added to a solution of 96 mg (0.27 mmol) of the sulfonamide obtained in d) above in a mixture of 0.15 ml (1.85 mmol) of pyridine and 2 ml of methylene chloride, and the whole was stirred overnight at room temperature. After the reaction had been allowed to go to completion, water was added to the reaction mixture which was then extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate, and then the solvent was removed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography, using 10 g of silica gel with ethyl acetate as the eluent, to yield 32 mg of the title compound as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.48 (3H, singlet),
3.08 (3H, singlet),
3.84 (2H, singlet),
5.51 (2H, singlet),
7.10-7.85 (11H, multiplet).

EXAMPLE 97

5-[(9-Benzyl-4-methyl-1-methylthiocarbazol)-2-yl-
methyl]-1H-tetrazole

The title compound was prepared following a similar

procedure to that of Examples 75 - 77, but starting with 9-benzyl-4-methylthiocarbazol-2-acetic acid. The title compound was obtained as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

1.91 (3H, singlet),
2.87 (3H, singlet),
4.76 (2H, singlet),
6.34 (2H, doublet, $J = 17\text{Hz}$),
6.9-7.0 (2H, multiplet),
7.08 (1H, singlet),
7.2-7.5 (6H, multiplet),
8.21 (1H, doublet, $J = 8\text{Hz}$).

EXAMPLE 98

Methyl 4-(indol-1-yl)methylbenzoate

Following a procedure and using relative proportions of starting materials similar to those described in Example 65, but using indole and methyl 4-(bromomethyl)-benzoate as starting material, the title compound was obtained as a solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.88 (3H, singlet),
5.37 (2H, singlet),
6.57 (1H, doublet, $J = 3.2\text{ Hz}$),
7.10-7.30 (7H, multiplet),
7.68 (1H, doublet, $J = 6.2\text{ Hz}$),
8.05 (2H, doublet, $J = 8.2\text{ Hz}$).

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EXAMPLE 994-(Indol-1-yl)methylbenzoic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 83, but using methyl 4-(indol-1-yl)methyl benzoate as starting material, the title compound was obtained as a solid melting at 163 - 165°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

5.41 (2H, singlet),
6.60 (1H, doublet, $J = 3.3$ Hz),
7.05-7.30 (6H, multiplet),
7.68 (1H, doublet, $J = 6.2$ Hz),
8.03 (2H, doublet, $J = 8.2$ Hz).

EXAMPLE 1005-[4-(Indol-1-yl)methyl]phenyl-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Examples 75 - 77, but using 4-(indol-1-yl)methylbenzoic acid as starting material, the title compound was obtained as a solid melting at 181 - 184°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 and tetradeuterated methanol, 270MHz), δ ppm:

5.40 (2H, singlet),
6.59 (1H, doublet, $J = 3.2$ Hz),
7.05-7.30 (6H, multiplet),
7.68 (1H, doublet, $J = 6.2$ Hz),
7.98 (2H, doublet, $J = 8.2$ Hz).

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EXAMPLE 1011-(4-Phenylbenzyl)-4-cyanoindole

Following a procedure and using relative proportions of starting materials similar to those described in Example 65, but using 4-cyanoindole and 4-phenylbenzyl-chloride as starting materials, the title compound was obtained as a solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

5.40 (2H, singlet),

6.78 (1H, doublet, $J = 3.0$ Hz),

7.10-7.60 (13H, multiplet).

EXAMPLE 1022-[1-(4-Phenylbenzyl)indol-4-yl]acetic Acid

Following procedures and using relative proportions of starting materials similar to those described in Examples 89, 90 and 91, but using 1-(4-phenylbenzyl)-4-cyanoindole as starting material, the title compound was obtained as a solid melting at 159 - 160°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.94 (2H, singlet),

5.36 (2H, singlet),

6.62 (1H, doublet, $J = 3.2$ Hz),

7.04 (1H, doublet, $J = 7.1$ Hz),

7.10-7.60 (12H, multiplet).

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EXAMPLE 1032-(9-Benzyl-4-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]-indol-2-yl)acetic Acid

Following procedures and using relative proportions of starting materials similar to those described in Examples 78, 79, 80, 81, 82 and 83, but using 3-tert-butyl-diphenylsilyloxy-1-butanol as starting material, the title compound was obtained as a solid melting at 158 - 162°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.44 (3H, doublet, $J = 6.8$ Hz),
- 2.10-2.20 (2H, multiplet),
- 2.76 (2H, doublet, $J = 7.0$ Hz),
- 3.25-3.40 (1H, multiplet),
- 3.80-3.95 (1H, multiplet),
- 5.20 (2H, singlet),
- 7.05-7.60 (9H, multiplet).

EXAMPLE 1045-(9-Benzyl-4-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]-indol-2-yl)methyl-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Example 84, but using 2-(9-benzyl-4-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)acetic acid as starting material, the title compound was obtained as a solid melting at 176 - 178°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 and tetradeuterated methanol, 270MHz), δ ppm:

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1.41 (3H, doublet, $J = 6.9$ Hz),
2.03-2.25 (2H, multiplet),
3.25-3.45 (3H, multiplet),
3.90-4.05 (1H, multiplet),
5.18 (2H, singlet),
7.05-7.60 (9H, multiplet).

EXAMPLE 105

1-Benzyl-2,3-dimethyl-6-acetylindole

Following a procedure and using relative proportions of starting materials similar to those described in Examples 40 and 65 but using 2,3-dimethylindole as starting material, the title compound was obtained as a solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.30 (6H, singlet),
2.62 (3H, singlet),
5.37 (2H, singlet),
6.95 (1H, doublet, $J = 2.0$ Hz),
7.20-7.30 (4H, multiplet),
7.53 (1H, doublet, $J = 8.4$ Hz),
7.71 (1H, doublet, $J = 8.4$ Hz),
7.92 (1H, singlet).

EXAMPLE 106

2-(1-Benzyl-2,3-dimethylindol-6-yl)acetic Acid

Following procedures and using relative proportions of starting materials similar to those described in Example 89, 90 and 91, but using 1-benzyl-2,3-dimethyl-

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6-acetylundole as starting material, the title compound was obtained as a solid melting at 137°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.25 (6H, singlet),

3.69 (2H, singlet),

5.27 (2H, singlet),

6.90-7.50 (8H, multiplet).

EXAMPLE 107

5-(1-Benzyl-2,3-dimethylindol-6-yl)methyl-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Examples 75, 76 and 77, but using (1-benzyl-2,3-dimethyl-indol-6-yl)acetic acid as starting material, the title compound was obtained as a solid melting at 160 - 163°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 and tetradeuterated methanol, 270MHz), δ ppm:

2.26 (3H, singlet),

2.27 (3H, singlet),

4.33 (2H, singlet),

5.26 (2H, singlet),

6.90-7.30 (7H, multiplet),

7.46 (1H, doublet, $J = 8.0$ Hz).

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EXAMPLE 1085-(9-Benzylcarbazol-2-yl)methyl-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Examples 75, 76 and 77, but using 2-(9-benzylcarbazole-2-yl)acetic acid as starting material, the title compound was obtained as a solid melting at 175 - 184°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 and tetradeuterated methanol, 270MHz), δ ppm:

4.44 (2H, singlet),
5.50 (2H, singlet),
7.05-7.45 (10H, multiplet),
8.08 (2H, triplet, $J = 7.8$ Hz).

EXAMPLE 109Diethyl (9-Benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)-malonate

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 48, but using N,N-benzylphenylhydrazine and diethyl 3-oxocyclohexylmalonate as starting materials.

EXAMPLE 110(9-Benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)malonic acid

The title compound was obtained by following a procedure and using relative proportions of starting

materials similar to those described in Example 26, but using diethyl (9-benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)malonate as starting material.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

1.6-1.9 (1H, multiplet),
2.1-2.4 (1H, multiplet),
2.5-3.0 (5H, multiplet),
3.39 (1H, doublet, $J = 8.4$ Hz),
5.23 (2H, singlet),
6.9-7.6 (9H, multiplet).

EXAMPLE 111

(9-Benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)acetic Acid

A solution of 200mg of (9-benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)malonic acid, obtained as described in Example 110, in 5 ml of N,N-dimethylformamide was refluxed for 2 hours. The solvent was evaporated under reduced pressure. The resulting residue was subjected to column chromatography using 5 g of silica gel with a 1 : 2 v/v mixture of ethyl acetate and hexane as the eluent, then recrystallized from ethyl acetate and hexane, to yield 162 mg of the title compound.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

1.5-1.8 (1H, multiplet),
2.0-2.2 (1H, multiplet),
2.3-2.6 (4H, multiplet),
2.7-3.0 (3H, multiplet),
5.24 (2H, singlet),
6.9-7.3 (8H, multiplet),
7.4-7.6 (1H, multiplet).

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EXAMPLE 112(Ethyl 9-Benzyl-4-oxo-1,2,3,4-tetrahydrocarbazol-3-yl)-
acetate

227 mg of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in 2 ml of tetrahydrofuran was added dropwise, with ice-cooling, to a solution of 174 mg of ethyl (9-benzyl-1,2,3,4-tetrahydrocarbazol-3-yl)acetate, obtained as described in Example 62, in 4.5 ml of tetrahydrofuran and 0.5 ml of water. The reaction mixture was stirred for 10 minutes. A saturated aqueous solution of sodium chloride was then added to the reaction mixture, the aqueous layer was extracted with ethyl acetate, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 8 g of silica gel using a 2 : 3 v/v mixture of ethyl acetate and hexane as the eluent, then recrystallized from ethyl acetate and hexane, to yield 169 mg of the title compound.

EXAMPLE 113(9-Benzyl-4-oxo-1,2,3,4-tetrahydrocarbazol-3-yl)acetic
Acid

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl (9-benzyl-4-oxo-1,2,3,4-tetrahydrocarbazol-3-yl)acetate as starting material.

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Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm
2.0-2.2 (1H, multiplet),
2.3-2.5 (1H, multiplet),
2.45 (1H, doublet, $J = 11.3$ Hz),
2.9-3.2 (4H, multiplet),
5.35 (2H, singlet),
7.0-7.1 (2H, multiplet),
7.2-7.4 (6H, multiplet),
8.26 (1H, doublet, $J = 6.6$ Hz).

EXAMPLE 114

Isopropyl (1-Methylthio-4-propylcarbazol-2-yl)acetate

The title compound was obtained by following procedures and using relative proportions of starting materials similar to those described in Examples 1 and 2, but using 1,1-bismethylthio-2-oxo-4-propyl-1,2,3,4-tetrahydrocarbazole as starting material.

EXAMPLE 115

Isopropyl (9-Benzyl-1-methylthio-4-propylcarbazol-2-yl)- acetate

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 13, but using isopropyl (1-methylthio-4-propylcarbazol-2-yl)-acetate as starting material.

EXAMPLE 116(9-Benzyl-1-methylthio-4-propylcarbazol-2-yl)acetic Acid

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-1-methylthio-4-propylcarbazol-2-yl)acetate as starting material.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm

1.13 (3H, triplet, $J = 7.4$ Hz),

1.8-2.0 (1H, multiplet),

1.97 (3H, singlet),

3.20 (3H, triplet, $J = 7.8$ Hz),

4.15 (2H, singlet),

6.40 (2H, singlet),

7.0-7.5 (8H, multiplet),

8.0-8.2 (2H, multiplet).

EXAMPLE 117Isopropyl 2-(9-Benzyl-1-methylthio-4-propylcarbazol-2-yl)-3-phenylpropionate

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 13, but using isopropyl (1-methylthio-4-propylcarbazol-2-yl)-acetate as starting material.

EXAMPLE 1182-(9-Benzyl-1-methylthio-4-propylcarbazol-2-yl)-3-phenylpropionic Acid

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl 2-(9-benzyl-1-methylthio-4-propylcarbazol-2-yl)-3-phenylpropionate as starting material.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm

- 1.12 (3H, triplet, $J = 7.3$ Hz),
- 1.84 (3H, singlet),
- 1.8-2.0 (1H, multiplet),
- 3.05 (1H, doublet of doublets, $J = 13.7$ Hz,
 $J = 7.2$ Hz),
- 3.1-3.4 (2H, multiplet),
- 3.47 (1H, doublet of doublets, $J = 13.7$ Hz,
 $J = 7.8$ Hz),
- 5.37 (1H, triplet, $J = 7.5$ Hz),
- 6.35 (2H, singlet),
- 6.9-7.5 (14H, multiplet),
- 8.11 (1H, doublet, $J = 7.9$ Hz).

EXAMPLE 119tert-Butyl (1-Methylthio-4-propylcarbazol-2-yl)oxyacetate

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 43, but using 2-hydroxy-1-methylthio-4-propylcarbazole as starting material.

EXAMPLE 120(1-Methylthio-4-propylcarbazol-2-yl)oxyacetic Acid

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using tert-butyl (1-methylthio-4-propylcarbazol-2-yl)-oxyacetate as starting material.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm

1.10 (3H, triplet, $J = 7.4$ Hz),
1.8-2.0 (1H, multiplet),
2.43 (3H, singlet),
3.15 (2H, triplet, $J = 7.7$ Hz),
4.86 (2H, singlet),
6.63 (1H, singlet),
7.26 (1H, triplet, $J = 7.6$ Hz),
7.41 (1H, triplet, 7.6 Hz),
7.49 (1H, doublet, $J = 7.6$ Hz),
8.00 (1H, doublet, $J = 7.6$ Hz),
8.62 (1H, broad singlet).

EXAMPLE 121Methyl (9-Benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)acetate

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 85, but using (9-benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)acetic acid and diazomethane as starting materials.

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EXAMPLE 122Methyl (9-Benzyl-4-oxo-1,2,3,4-tetrahydrocarbazol-2-yl) -
acetate

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 112, but using methyl (9-benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)-acetate and diazomethane as starting materials.

EXAMPLE 123(9-Benzyl-4-oxo-1,2,3,4-tetrahydrocarbazol-2-yl) -
acetic Acid

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using methyl (9-benzyl-4-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)acetate as starting material.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm
2.3-3.0 (6H, multiplet),
3.17 (1H, doublet of doublets, $J = 16.4\text{Hz}$,
 $J = 4.4\text{Hz}$),
5.35 (2H, singlet),
6.9-7.1 (2H, multiplet),
7.2-7.4 (6H, multiplet),
8.27 (1H, doublet, $J = 8.0\text{Hz}$).

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EXAMPLE 124[1-(3-Benzylloxybenzyl)indol-4-yl]thioacetomorpholide

Following procedures and using relative proportions of starting materials similar to those described in Examples 88, 89 and 90, but using 3-benzylloxybenzyl chloride as a starting material, the title compound was obtained as an amorphous solid.

EXAMPLE 125[1-(3-Benzylloxybenzyl)indol-4-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using [1-(3-benzylloxybenzyl)indol-4-yl]-thioacetomorpholide, as obtained in Example 124, as a starting material, the title compound was obtained as a solid melting at 130-133°C and in a yield of 80%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

3.93 (2H, singlet);

4.97 (2H, singlet);

5.27 (2H, singlet);

6.57 - 7.40 (14H, multiplet).

EXAMPLE 126[1-(4-Pyridylmethyl)indol-4-yl]thioacetomorpholide

Following procedures and using relative proportions of starting materials similar to those described in Examples 88, 89 and 90, but using 4-pyridylmethyl chloride as a starting material, the title compound was obtained as an amorphous solid.

EXAMPLE 127[1-(4-Pyridylmethyl)indol-4-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using [1-(4-pyridylmethyl)indol-4-yl]thio- acetomorpholide, as obtained in Example 126, as a starting material, the title compound was obtained in a yield of 79% as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 + tetradeuterated methanol, 270MHz), δ ppm:

3.81 (2H, singlet);
5.32 (2H, singlet);
6.68 (1H, doublet, $J = 3.5\text{Hz}$);
6.92 - 7.13 (6H, multiplet);
8.41 (2H, doublet, $J = 6.4\text{Hz}$).

EXAMPLE 1285-[1-(3-Benzyloxybenzyl)indol-4-yl]methyl-1H-tetrazole

Following procedures and using relative proportions

of starting materials similar to those described in Examples 75, 76 and 77, but using [1-(3-benzyloxybenzyl)-indol-4-yl]acetic acid, as obtained in Example 125, as a starting material, the title compound was obtained as a solid melting at 172-174°C

Nuclear Magnetic Resonance Spectrum (CDCl_3 + tetradeuterated methanol, 270MHz), δ ppm:

4.58 (2H, singlet);
4.98 (2H, singlet);
5.29 (2H, singlet);
6.46 (1H, doublet, $J = 3.2\text{Hz}$);
6.70 (1H, singlet);
6.71 (1H, doublet, $J = 7.1\text{Hz}$);
6.87 (1H, doublet of doublets, $J = 8.7, 1.9\text{Hz}$);
7.00 (1H, doublet, $J = 7.3\text{Hz}$);
7.1 - 7.4 (9H, multiplet).

EXAMPLE 129

(1-Diphenylmethylinol-4-yl)thioacetomorpholide

Following procedures and using relative proportions of starting materials similar to those described in Examples 88, 89 and 90, but using diphenylmethyl bromide as a starting material, the title compound was obtained, as an oil.

EXAMPLE 130

(1-Diphenylmethylinol-4-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using (1-diphenylmethylinol-4-yl)thio-

acetomorpholide, as obtained in Example 129, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 170-175°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

6 ppm:

3.92 (2H, singlet);

6.53 (2H, doublet, $J = 3.3\text{Hz}$);

6.81 (1H, singlet);

6.84 (1H, doublet, $J = 3.3\text{Hz}$);

7.0 - 7.4 (13H, multiplet).

EXAMPLE 131

Methyl (9-Benzyl-4-methyl-1-propoxycarbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 220, but using iodopropane as a starting material, the title compound was obtained in a yield of 90% as an oil.

EXAMPLE 132

(9-Benzyl-4-methyl-1-propoxycarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl (9-benzyl-4-methyl-1-propoxycarbazol-2-yl)acetate, as obtained in Example 131, as a starting material, the title compound was obtained in a yield of 88% as a solid melting at 175-177°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

0.82 (3H, triplet, $J = 7.5\text{Hz}$);
1.67 (2H, sextet, $J = 7.2\text{Hz}$);
2.84 (3H, singlet);
3.67 (2H, triplet, $J = 6.9\text{Hz}$);
3.84 (2H, singlet);
5.89 (2H, singlet);
6.92 (1H, singlet);
7.02 - 7.42 (8H, multiplet);
8.17 (1H, doublet, $J = 7.4\text{Hz}$).

EXAMPLE 133

Methyl (9-Benzyl-1-benzyloxy-4-methylcarbazol-2-yl)- acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 220, but using benzyl bromide as a starting material, the title compound was obtained in a yield of 93% as an oil.

EXAMPLE 134

(9-Benzyl-1-benzyloxy-4-methylcarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl (9-benzyl-1-benzyloxy-4-methylcarbazol-2-yl)acetate, as obtained in Example 133, as a starting material, the title compound was obtained in a yield of 88% as a solid melting at 187-191°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.86 (3H, singlet);
3.86 (2H, singlet);
4.81 (2H, singlet);
5.86 (2H, singlet);
6.90 - 7.42 (14H, multiplet);
8.19 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 135

tert-Butyl [9-(3-Benzyloxybenzyl)-4-methyl-1-methylthio-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 3-benzyloxybenzyl chloride as starting materials, the title compound was obtained in a yield of 78% as an oil.

EXAMPLE 136

[9-(3-Benzyloxybenzyl)-4-methyl-1-methylthio-carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(3-benzyloxybenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 135, as a starting material, the title compound was obtained in a yield of 85% as a solid melting at 178-180°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

1.92 (3H, singlet);
2.89 (3H, singlet);
4.19 (2H, singlet);
4.90 (2H, singlet);
6.33 (2H, singlet);
6.6 - 7.5 (13H, multiplet);
8.18 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 137

5-[9-(3-Benzoyloxybenzyl)-4-methyl-1-methylthio-
carbazol-2-yl]methyl-1H-tetrazole

Following procedures and using relative proportions of starting materials similar to those described in Examples 75, 76 and 77, but using [9-(3-benzoyloxybenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetic acid, as obtained in Example 136, as a starting material, the title compound was obtained as a solid melting at 205-207°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

1.86 (3H, singlet);
2.87 (3H, singlet);
4.78 (2H, singlet);
4.92 (2H, singlet);
6.34 (2H, singlet);
6.60 - 7.50 (13H, multiplet);
8.20 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 138tert-Butyl [4-Methyl-1-methylthio-9-(3-nitrobenzyl)]-
carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 3-nitrobenzyl bromide as starting materials, the title compound was obtained in a yield of 83% as an oil.

EXAMPLE 139[4-Methyl-1-methylthio-9-(3-nitrobenzyl)carbazol-2-yl]-
acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [4-methyl-1-methyl-9-(3-nitrobenzyl)thiocarbazol-2-yl]acetate, as obtained in Example 138, as a starting material, the title compound was obtained in a yield of 98% as a solid melting at 196-201°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

- 2.02 (3H, singlet);
- 2.90 (3H, singlet);
- 4.19 (2H, singlet);
- 6.42 (2H, singlet);
- 7.09 (1H, singlet);
- 7.15 - 7.50 (5H, multiplet);
- 8.06 (1H, doublet, J = 6.6Hz);
- 8.07 (1H, singlet);
- 8.21 (1H, doublet, J = 7.7Hz).

EXAMPLE 140tert-Butyl [9-(3-Fluorobenzyl)-4-methyl-1-methylthio-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 3-fluorobenzyl bromide as starting materials, the title compound was obtained in a yield of 90% as an oil.

EXAMPLE 141[9-(3-Fluorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]-acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(3-fluorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 140, as a starting material, the title compound was obtained in a yield of 97% as a solid melting at 195-202°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.98 (3H, singlet);
- 2.89 (3H, singlet);
- 4.20 (2H, singlet);
- 6.36 (2H, singlet);
- 6.70 - 6.90 (3H, multiplet);
- 7.07 (1H, singlet);
- 7.15 - 7.50 (4H, multiplet);
- 8.20 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 142tert-Butyl [9-(4-Fluorobenzyl)-4-methyl-1-methylthio-
carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthiocarbazol-2-yl)acetate and 4-fluorobenzyl bromide as starting materials, the title compound was obtained in a yield of 91% as an oil.

EXAMPLE 143[9-(4-Fluorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]-
acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(4-fluorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 142, as a starting material, the title compound was obtained in a yield of 97% as a solid melting at 189-194°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

- 1.98 (3H, singlet);
- 2.89 (3H, singlet);
- 4.20 (2H, singlet);
- 6.33 (2H, singlet);
- 6.85 - 7.03 (4H, multiplet);
- 7.06 (1H, singlet);
- 7.25 - 7.50 (3H, multiplet);
- 8.19 (1H, doublet, J = 8.0Hz).

EXAMPLE 144tert-Butyl [9-(3-Chlorobenzyl)-4-methyl-1-methylthio-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 3-chlorobenzyl bromide as starting materials, the title compound was obtained in a yield of 86% as an oil.

EXAMPLE 145[9-(3-Chlorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]-acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(3-chlorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 144, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 205-210°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

- 1.97 (3H, singlet);
- 2.89 (3H, singlet);
- 4.19 (2H, singlet);
- 6.33 (2H, singlet);
- 6.85 (1H, doublet, J = 6.5Hz);
- 7.06 (1H, singlet);
- 7.10 - 7.50 (6H, multiplet);
- 8.19 (1H, doublet, J = 7.8Hz).

EXAMPLE 146

tert-Butyl {9-[(1-Methyl-2-pyridon-4-yl)methyl]-4-methyl-1-methylthiocarbazol-2-yl}acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthiocarbazol-2-yl)acetate and chloro(1-methyl-2-pyridon-4-yl)methane as starting materials, the title compound was obtained in a yield of 87% as an oil.

EXAMPLE 147

{9-[(1-Methyl-2-pyridon-4-yl)methylbenzyl]-4-methyl-1-methylthiocarbazol-2-yl}acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl {9-[(1-methyl-2-pyridon-4-yl)methylbenzyl]-4-methyl-1-methylthiocarbazol-2-yl}acetate, as obtained in Example 146, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 188-197°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 + tetradeuterated methanol, 270MHz), δ ppm:

- 2.16 (3H, singlet);
- 2.88 (3H, singlet);
- 3.46 (3H, singlet);
- 4.14 (2H, singlet);
- 5.91 (1H, doublet of doublets, $J = 7.1, 1.9\text{Hz}$);
- 6.17 (1H, singlet);
- 6.22 (2H, singlet);
- 7.08 (1H, singlet);
- 7.18 (1H, doublet, $J = 7.0\text{Hz}$);

7.20 - 7.54 (3H, multiplet);
8.18 (1H, doublet, $J = 8.1\text{Hz}$).

EXAMPLE 148

tert-Butyl [9-(3,4-Dichlorobenzyl)-4-methyl-1-methylthio-
carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 3,4-dichlorobenzyl chloride as starting materials, the title compound was obtained in a yield of 82% as an oil.

EXAMPLE 149

[9-(3,4-Dichlorobenzyl)-4-methyl-1-methylthio-
carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(3,4-dichlorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 148, as a starting material, the title compound was obtained in a quantitative yield, as a solid melting at 110-120°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.02 (3H, singlet);
2.89 (3H, singlet);
4.20 (2H, singlet);
6.30 (2H, singlet);
6.80 (1H, doublet of doublets, $J = 8.5, 1.9\text{Hz}$);

7.07 (1H, singlet);
7.21 (1H, doublet, J = 1.9Hz);
7.26 - 7.50 (4H, multiplet);
8.19 (1H, doublet, J = 7.4Hz).

EXAMPLE 150

tert-Butyl [9-Methylsulfonyl-4-methyl-1-methylthio- carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and methylsulfonyl chloride as starting materials, the title compound was obtained in a yield of 95% as an oil.

EXAMPLE 151

(9-Methylsulfonyl-4-methyl-1-methylthiocarbazol-2-yl)- acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl (9-methylsulfonyl-4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 150, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 217-218°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 +
tetra-deuterated methanol, 270MHz), δ ppm:

2.22 (3H, singlet);
2.78 (3H, singlet);
3.53 (3H, singlet);

4.15 (2H, singlet);
7.30 (1H, singlet);
7.37 - 7.50 (2H, multiplet);
7.90 (1H, doublet, J = 7.6Hz);
8.00 (1H, doublet, J = 8.1Hz).

EXAMPLE 152

5-[9-(3,4-Dichlorobenzyl)-4-methyl-1-methylthio-
carbazol-2-yl]methyl-1H-tetrazole

Following procedures and using relative proportions of starting materials similar to those described in Examples 75, 76 and 77, but using [9-(3,4-dichlorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetic acid, as obtained in Example 149, as a starting material, the title compound was obtained as a solid melting at 242-245 °C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 +
tetra deuterated methanol, 270MHz), δ ppm:

1.97 (3H, singlet);
2.87 (3H, singlet);
4.79 (2H, singlet);
6.30 (2H, singlet);
6.81 (1H, doublet of doublets, J = 8.6, 1.9Hz);
7.05 (1H, singlet);
7.18 (1H, doublet, J = 1.7Hz);
7.28 - 7.35 (5H, multiplet).

EXAMPLE 153Isopropyl (1-Methylthio-4-propylcarbazol-2-yl)acetatea) Ethyl 3-(indol-3-yl)hexanoate

10.7 g (148 mmol) of butanal was added gradually to 300 ml of a solution of 11.6 g of indole (98.6 mmol) and 14.2 g of Meldrum's acid (98.6 mmol) in acetonitrile at room temperature. 500 mg of proline was added to the reaction mixture which was then stirred overnight. The solvent was removed by evaporation under reduced pressure. The residue was dissolved in 200 ml of pyridine, and 15 ml of ethanol and 2.5 g of copper powder were added to the resulting solution. The reaction mixture was then refluxed for 4 hours and the copper powder was filtered off after this time. The solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 15% v/v solution of ethyl acetate in hexane) to yield 20.1 g (78%) of the title compound as an oil.

b) 1,1-Bismethylthio-4-propyl-1,2,3,4-tetrahydro-carbazol-2-one

Following procedures and using relative proportions of starting materials similar to those described in Examples 1a) and 1b), but using ethyl 3-(indol-3-yl)-hexanoate, as obtained in a) above, as a starting material, the title compound was obtained as an amorphous solid.

c) Isopropyl (2-hydroxy-1,1-bismethylthio-4-propyl-1,2,3,4-tetrahydrocarbazol-2-yl) acetate

Following a procedure and using relative proportions

of starting materials similar to those described in Example 1d), but using 1,1-bismethylthio-4-propyl-1,2,3,4-tetrahydrocarbazol-2-one, as obtained in b) above, and isopropyl acetate as starting materials, the title compound was obtained in a yield of 81% as an oil.

d) Isopropyl (1-methylthio-4-propylcarbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 2, but using isopropyl (2-hydroxy-1,1-bismethylthio-4-propyl-1,2,3,4-tetrahydrocarbazol-2-yl)acetate, as obtained in c) above, as a starting material, the title compound was obtained in a yield of 89% as an amorphous solid.

EXAMPLE 154

(1-Methylcarbazol-2-yl)thioacetomorpholide

a) 2-Acetyl-1-methylcarbazole

15 ml of a 1.5 M solution of methyllithium (22mmol) in diethyl ether was added to 30 ml of a solution of 1.25 g of 1-methylcarbazol-2-ylcarboxylic acid (5.5 mmol - as obtained in Example 26) in diethyl ether, at a temperature of -78°C. The reaction mixture was then warmed to room temperature and stirred for 1 hour. After this time, the mixture was poured into a 0.5 N aqueous solution of hydrogenchloride. The aqueous layer was extracted with ethyl acetate and the resulting organic layer was washed successively with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, in that order, dried over anhydrous magnesium sulfate, and the solvent was then removed by evaporation under reduced

pressure. The residue was subjected to column chromatography (eluent: a 25% v/v solution of ethyl acetate in hexane) to yield 1.08 g (88%) of the title compound as an amorphous solid.

b) (1-Methylcarbazol-2-yl)thioacetomorpholide

Following a procedure and using relative proportions of starting materials similar to those described in Example 38, but using 2-acetyl-1-methylcarbazole, as obtained in a) above, as a starting material, the title compound was obtained in a yield of 75% as an oil.

EXAMPLE 155

(1-Methylcarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using (1-methylcarbazol-2-yl)thioacetomorpholide, as obtained in Example 154, as a starting material, the title compound was obtained in a yield of 85% as a solid melting at 121°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 2.51 (3H, singlet);
- 3.86 (2H, singlet);
- 7.11 (1H, doublet, $J = 7.9\text{Hz}$);
- 7.22 (1H, triplet, $J = 7.9\text{Hz}$);
- 7.3 - 7.5 (2H, multiplet);
- 7.88 (1H, doublet, $J = 7.9\text{Hz}$);
- 8.01 (1H, broad singlet);
- 8.03 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 156[9-(3-Nitrobenzyl)carbazol-2-yl]acetomorpholidea) Carbazol-2-ylacetomorpholide

An excess of a 1 N aqueous solution of potassium hydroxide was added to 50 ml of an ethanolic solution of 3.10 g of (carbazol-2-yl)thioacetomorpholide (10 mmol), as obtained in Example 38, and the reaction mixture was stirred overnight at room temperature. The aqueous layer was then acidified by adding a 0.5 N aqueous solution of hydrogen chloride to the mixture, and the reaction mixture was then extracted with ethyl acetate. The resulting organic layer was washed successively with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, in that order, dried over anhydrous magnesium sulfate, and the solvent was then removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: an 80% v/v solution of ethyl acetate in hexane) to yield 2.54 g (86%) of the title compound as an amorphous solid.

b) [9-(3-Nitrobenzyl)carbazol-2-yl]acetomorpholide

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using (carbazol-2-yl)acetomorpholide, as obtained in a) above, and 3-nitrobenzyl bromide as starting materials, the title compound was obtained in a yield of 83% as an amorphous solid.

EXAMPLE 157[9-(3-Nitrobenzyl)carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using [9-(3-nitrobenzyl)carbazol-2-yl]-acetomorpholide, as obtained in Example 156, as a starting material, the title compound was obtained in a yield of 81% as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.55 (2H, singlet);

5.17 (2H, singlet);

6.9 - 7.4 (7H, multiplet);

7.6 - 7.9 (4H, multiplet).

EXAMPLE 158Methyl [9-(3-Acetamidobenzyl)carbazol-2-yl]acetate

a) Methyl [9-(3-Nitrobenzyl)carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 1a), but using [9-(3-nitrobenzyl)carbazol-2-yl]-acetic acid, as obtained in Example 157, as a starting material, the title compound was obtained in a quantitative yield as an oil.

b) Methyl [9-(3-Acetamidobenzyl)carbazol-2-yl]acetate

20 mg of a 10% w/w preparation of palladium-on-carbon were added to 2 ml of a 1 : 1 v/v mixture of ethanol and tetrahydrofuran in which were dissolved

114 mg of methyl [9-(3-nitrobenzyl)carbazol-2-yl]acetate (0.30 mmol), as obtained in a) above. The reaction mixture was then stirred for 3 hours at room temperature under a stream of hydrogen. After this time, the catalyst was filtered off, and the solvent was removed by evaporation under reduced pressure to yield an amine compound. The thus obtained compound was dissolved in 0.5 ml of pyridine and then 0.5 ml of anhydrous acetic acid was added to the resulting solution. The reaction mixture was stirred for 30 min at room temperature and then an excess of water was added. The aqueous layer was extracted with ethyl acetate and the resulting organic layer was washed successively with a diluted aqueous solution of hydrogen chloride and a saturated aqueous solution of sodium chloride, in that order, dried over anhydrous magnesium sulfate, and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 40% v/v solution of ethyl acetate in hexane) to yield 110 mg (93%) of the title compound as an oil.

EXAMPLE 159

[9-(3-Acetamidobenzyl)carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl [9-(3-acetamidobenzyl)carbazol-2-yl]acetate, as obtained in Example 158, as a starting material, the title compound was obtained in a yield of 98% as a solid melting at 138-140°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

2.06 (3H, singlet);
3.76 (2H, singlet);
5.49 (2H, singlet);
6.94 (1H, doublet, J = 7.3Hz);
7.06 (1H, singlet);
7.1 - 7.4 (6H, multiplet);
7.67 (1H, doublet, J = 7.9Hz);
8.0 - 8.1 (2H, multiplet).

EXAMPLE 160

[9-(4-Benzyloxybenzyl)carbazol-2-yl]acetomorpholide

Following a procedure and using relative proportions of starting materials similar to those described in Example 156 b), but using 4-benzyloxybenzyl chloride, as a starting material, the title compound was obtained in a yield of 77% as an amorphous solid.

EXAMPLE 161

[9-(4-Benzyloxybenzyl)carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using [9-(4-benzyloxybenzyl)carbazol-2-yl]acetomorpholide, as obtained in Example 160, as a starting material, the title compound was obtained in a yield of 90% as a solid melting at 169-171°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

3.81 (2H, singlet);
4.98 (2H, singlet);
5.44 (2H, singlet);

6.85 (2H, doublet, J = 8.7Hz);
7.07 (2H, doublet, J = 8.7Hz);
7.1 - 7.5 (10H, multiplet);
8.0 - 8.1 (2H, multiplet).

EXAMPLE 162

Methyl [9-(4-Hydroxybenzyl)carbazol-2-yl]acetate

a) Methyl [9-(4-benzyloxybenzyl)carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 1a), but using [9-(4-benzyloxybenzyl)carbazol-2-yl]acetic acid, as obtained in Example 161, as a starting material, the title compound was obtained in a quantitative yield as an oil.

b) Methyl [9-(4-hydroxybenzyl)carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 52, but using methyl [9-(4-benzyloxybenzyl)-carbazol-2-yl]acetate, as obtained in a) above, as a starting material, the title compound was obtained in a yield of 75% as an oil.

EXAMPLE 163

[9-(4-Hydroxybenzyl)carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl [9-(4-hydroxybenzyl)-carbazol-2-yl]acetate, as obtained in Example 162, as a

starting material, the title compound was obtained in a quantitative yield as a solid melting at 216°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.80 (2H, singlet);
5.44 (2H, singlet);
6.75 (2H, doublet, $J = 8.5\text{Hz}$);
7.02 (2H, doublet, $J = 8.5\text{Hz}$);
7.1 - 7.3 (2H, multiplet);
7.3 - 7.4 (3H, multiplet);
7.47 (1H, singlet);
8.0 - 8.1 (2H, multiplet).

EXAMPLE 164

[9-(3-Benzyloxybenzyl)carbazol-2-yl]acetomorpholide

Following a procedure and using relative proportions of starting materials similar to those described in Example 156 b), but using 3-benzyloxybenzyl chloride, as a starting material, the title compound was obtained in a yield of 79% as an amorphous solid.

EXAMPLE 165

[9-(3-Benzyloxybenzyl)carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using [9-(3-benzyloxybenzyl)carbazol-2-yl]acetomorpholide, as obtained in Example 164, as a starting material, the title compound was obtained in a yield of 89% as a solid melting at 154-156°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.79 (2H, singlet);

4.91 (2H, singlet);

5.45 (2H, singlet);

6.7 - 6.8 (2H, multiplet);

6.82 (1H, doublet of doublets, $J = 8.2, 2.0\text{Hz}$);

7.1 - 7.4 (10H, multiplet);

7.41 (1H, triplet, $J = 7.5\text{Hz}$);

8.0 - 8.1 (2H, multiplet).

EXAMPLE 166

Methyl [9-(3-Hydroxybenzyl)carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 162, but using [9-(3-benzyloxybenzyl)carbazol-2-yl]acetic acid, as obtained in Example 165, as a starting material, the title compound was obtained as an oil.

EXAMPLE 167

[9-(3-Hydroxybenzyl)carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl [9-(3-hydroxybenzyl)-carbazol-2-yl]acetate, as obtained in Example 166, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 186-187°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.79 (2H, singlet);
5.47 (2H, singlet);
6.54 (1H, singlet);
6.7 - 6.8 (2H, multiplet);
7.12 (1H, triplet, $J = 7.8\text{Hz}$);
7.1 - 7.5 (5H, multiplet);
8.0 - 8.1 (2H, multiplet).

EXAMPLE 168

(1-Methylthio-4-propylcarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (1-methylthio-4-propylcarbazol-2-yl)acetate, as obtained in Example 114, as a starting material, the title compound was obtained in a yield of 95% as a solid melting at 160-161°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

1.10 (3H, triplet, $J = 7.3\text{Hz}$);
1.8 - 1.9 (2H, multiplet);
2.34 (3H, singlet);
3.16 (2H, triplet, $J = 7.7\text{Hz}$);
4.17 (2H, singlet);
7.01 (1H, singlet);
7.26 (1H, triplet, $J = 7.7\text{Hz}$);
7.43 (1H, triplet, $J = 7.7\text{Hz}$);
7.51 (1H, doublet, $J = 7.7\text{Hz}$);
8.05 (1H, doublet, $J = 7.7\text{Hz}$);
8.70 (1H, broad singlet).

EXAMPLE 169Isopropyl [1-Methylthio-9-(3-nitrobenzyl)-4-propyl-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using isopropyl (1-methylthio-4-propyl-carbazol-2-yl)acetate, as obtained in Example 114, and 3-nitrobenzyl chloride as starting materials, the title compound was obtained in a yield of 80% as an oil.

EXAMPLE 170[1-Methylthio-9-(3-nitrobenzyl)-4-propylcarbazol-2-yl]-acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl [1-methylthio-9-(3-nitrobenzyl)-4-propylcarbazol-2-yl]acetate, as obtained in Example 169, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 150°C (with decomposition).

Nuclear Magnetic Resonance Spectrum [CDCl_3 + $(\text{CD}_3)_2\text{CO}$, 270MHz], δ ppm:

- 1.13 (3H, triplet, $J = 7.3\text{Hz}$);
- 1.8 - 2.0 (2H, multiplet);
- 2.02 (3H, singlet);
- 3.21 (2H, triplet, $J = 7.8\text{Hz}$);
- 4.20 (2H, singlet);
- 6.42 (2H, singlet);
- 7.09 (1H, singlet);
- 7.2 - 7.5 (5H, multiplet);
- 8.0 - 8.2 (3H, multiplet).

EXAMPLE 171Isopropyl 2-[1-Methylthio-9-(3-nitrobenzyl)-4-propyl-carbazol-2-yl]-3-(3-nitrophenyl)propionate

Following a procedure and using relative proportions of starting materials similar to those described in Example 16, but using isopropyl (1-methylthio-4-propyl-carbazol-2-yl)acetate, as obtained in Example 114, and 3-nitrobenzyl chloride as starting materials, the title compound was obtained in a yield of 88% as an oil.

EXAMPLE 1722-[1-Methylthio-9-(3-nitrobenzyl)-4-propyl-carbazol-2-yl]-3-(3-nitrophenyl)propionic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl 2-[1-methylthio-9-(3-nitrobenzyl)-4-propylcarbazol-2-yl]-3-(3-nitrophenyl)propionate, as obtained in Example 171, as a starting material, the title compound was obtained in a quantitative yield as an amorphous solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.12 (3H, triplet, $J = 7.4\text{Hz}$);
- 1.8 - 2.0 (2H, multiplet);
- 2.00 (3H, singlet);
- 3.1 - 3.3 (3H, multiplet);
- 3.56 (1H, doublet of doublets, $J = 13.9, 7.5\text{Hz}$);
- 5.38 (1H, triplet, $J = 7.5\text{Hz}$);
- 6.31 (1H, doublet, $J = 17.4\text{Hz}$);
- 6.40 (1H, doublet, $J = 17.4\text{Hz}$);
- 7.1 - 7.5 (7H, multiplet);

7.18 (1H, singlet);
7.9 - 8.2 (5H, multiplet).

EXAMPLE 173

Isopropyl [9-(3-acetamidobenzyl)-1-methylthio-4-propyl-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 158, but using isopropyl [1-methylthio-9-(3-nitrobenzyl)-4-propylcarbazol-2-yl]acetate, as obtained in Example 169, as a starting material, the title compound was obtained as an oil.

EXAMPLE 174

[9-(3-Acetamidobenzyl)-1-methylthio-4-propyl-carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl [9-(3-acetamidobenzyl)-1-methylthio-4-propylcarbazol-2-yl]acetate, as obtained in Example 173, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 130-134°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

1.14 (3H, triplet, J = 7.4Hz);
1.8 - 2.0 (2H, multiplet);
2.02 (3H, singlet);
2.07 (3H, singlet);
3.20 (2H, triplet, J = 7.8Hz);

4.20 (2H, singlet);
6.36 (2H, singlet);
6.76 (1H, doublet, J = 7.3Hz);
7.0 - 7.5 (6H, multiplet);
7.60 (1H, doublet, J = 8.0Hz);
8.10 (1H, doublet, J = 8.0Hz);
8.40 (1H, broad singlet).

EXAMPLE 175

Isopropyl [1-Methylthio-9-(4-nitrobenzyl)-4-propyl-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using isopropyl (1-methylthio-4-propyl-carbazol-2-yl)acetate, as obtained in Example 114, and 4-nitrobenzyl bromide as starting materials, the title compound was obtained in a yield of 76% as an oil.

EXAMPLE 176

[1-Methylthio-9-(4-nitrobenzyl)-4-propyl-carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl [1-methylthio-9-(4-nitrobenzyl)-4-propylcarbazol-2-yl]acetate, as obtained in Example 175, as a starting material, the title compound was obtained in a quantitative yield as an amorphous solid.

Nuclear Magnetic Resonance Spectrum [CDCl_3 + $(\text{CD}_3)_2\text{CO}$, 270MHz], δ ppm:

1.13 (3H, triplet, $J = 7.3\text{Hz}$);
1.8 - 2.0 (2H, multiplet);
1.99 (3H, singlet);
3.20 (2H, doublet of doublets, $J = 8.8, 6.9\text{Hz}$);
4.18 (2H, singlet);
6.43 (2H, singlet);
7.08 (1H, singlet);
7.18 (2H, doublet, $J = 8.9\text{Hz}$);
7.2 - 7.4 (1H, multiplet);
7.43 (1H, triplet, $J = 7.5\text{Hz}$);
8.0 - 8.2 (4H, multiplet).

EXAMPLE 177

Isopropyl [9-(4-Acetamidobenzyl)-1-methylthio-4-propyl-
carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 158 b), but using isopropyl [1-methylthio-9-(4-nitrobenzyl)-4-propylcarbazol-2-yl]acetate, as obtained in Example 175, as a starting material, the title compound was obtained as an oil.

EXAMPLE 178

[9-(4-Acetamidobenzyl)-1-methylthio-4-propyl-
carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl [9-(4-acetamidobenzyl)-1-methylthio-4-propylcarbazol-2-yl]acetate, as obtained in Example 177, as a starting material, the title compound was obtained in a quantitative yield as a solid

melting at 219-221°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.13 (3H, triplet, $J = 7.3\text{Hz}$);
- 1.8 - 2.0 (2H, multiplet);
- 2.12 (3H, singlet);
- 2.15 (3H, singlet);
- 3.20 (2H, triplet, $J = 7.8\text{Hz}$);
- 4.19 (2H, singlet);
- 6.35 (2H, singlet);
- 6.99 (2H, doublet, $J = 8.5\text{Hz}$);
- 7.08 (1H, singlet);
- 7.26 (1H, triplet, $J = 7.5\text{Hz}$);
- 7.3 - 7.5 (4H, multiplet);
- 7.88 (1H, broad singlet);
- 8.10 (1H, doublet, $J = 7.5\text{Hz}$).

EXAMPLE 179

tert-Butyl [9-(4-Chlorobenzyl)-4-methyl-1-methylthio-
carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 4-chlorobenzyl chloride as starting materials, the title compound was obtained in a yield of 92% as an oil.

EXAMPLE 180[9-(4-Chlorobenzyl)-4-methyl-1-methylthio-
carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(4-chlorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 179, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 198-199°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

1.99 (3H, singlet);
2.89 (3H, singlet);
4.19 (2H, singlet);
6.33 (2H, singlet);
6.95 (2H, doublet, $J = 8.4\text{Hz}$);
7.06 (1H, singlet);
7.19 (2H, doublet, $J = 8.4\text{Hz}$);
7.2 - 7.4 (2H, multiplet);
7.43 (1H, triplet, $J = 7.6\text{Hz}$);
8.19 (1H, doublet, $J = 7.6\text{Hz}$).

EXAMPLE 181Isopropyl [9-Benzyl-6-methoxy-4-methyl-1-methylthio-
carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 114, but using 5-methoxyindole and acetaldehyde as starting materials, the title compound was obtained as an oil.

EXAMPLE 182(9-Benzyl-6-methoxy-4-methyl-1-methylthio-carbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-6-methoxy-4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 181, as a starting material, the title compound was obtained in a yield of 97% as a solid melting at 205-206°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.95 (3H, singlet);
- 2.87 (3H, singlet);
- 3.92 (3H, singlet);
- 4.18 (2H, singlet);
- 6.34 (2H, singlet);
- 7.0 - 7.3 (8H, multiplet);
- 7.70 (1H, doublet, $J = 2.5\text{Hz}$).

EXAMPLE 183Isopropyl (9-Benzyl-5-methoxy-4-methyl-1-methylthio-carbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 114, but using 4-methoxyindole and acetaldehyde as starting materials, the title compound was obtained as an oil.

EXAMPLE 184(9-Benzyl-5-methoxy-4-methyl-1-methylthio-carbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-5-methoxy-4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 183, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 214-216°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

1.91 (3H, singlet);
2.99 (3H, singlet);
3.99 (3H, singlet);
4.15 (2H, singlet);
6.37 (2H, singlet);
6.69 (1H, doublet, $J = 8.1\text{Hz}$);
6.9 - 7.1 (4H, multiplet);
7.1 - 7.3 (3H, multiplet);
7.32 (1H, triplet, $J = 8.1\text{Hz}$).

EXAMPLE 185Isopropyl (9-Benzyl-6-hydroxy-4-methyl-1-methylthio-carbazol-2-yl)acetate

0.48 ml of a 1.0 M solution of boron tribromide (0.48 mmol) in methylene chloride was added to 1 ml of a solution of 106 mg isopropyl (9-benzyl-6-methoxy-4-methyl-1-methylthiocarbazol-2-yl)acetate (0.24 mmol), as obtained in Example 181, in methylene chloride, at a temperature of -78°C . The reaction mixture was then

warmed to at 0°C and stirred for 3 hours. After this time, the reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate, and the aqueous layer was extracted with methylene chloride. The resulting organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 15% v/v solution of ethyl acetate in hexane) to yield 81 mg (79%) of the title compound as an oil.

EXAMPLE 186

(9-Benzyl-6-hydroxy-4-methyl-1-methylthio-carbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-6-hydroxy-4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 185, as a starting material, the title compound was obtained in a yield of 94% as a solid melting at 219-222°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.99 (3H, singlet);
- 2.84 (3H, singlet);
- 4.17 (2H, singlet);
- 6.35 (2H, singlet);
- 7.0 - 7.4 (9H, multiplet);
- 7.69 (1H, singlet).

EXAMPLE 187Isopropyl (4-Isopropyl-1-methylthiocarbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 114, but using isobutyraldehyde as a starting material, the title compound was obtained as an oil.

EXAMPLE 188(4-Isopropyl-1-methylthiocarbazol-2-yl)acetic Acid.

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (4-isopropyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 187, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 171 - 173°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

1.47 (6H, doublet, $J = 6.8\text{Hz}$);
2.35 (3H, singlet);
3.91 (1H, sep, $J = 6.8\text{Hz}$);
4.19 (2H, singlet);
7.11 (1H, singlet);
7.25 (1H, triplet, $J = 7.7\text{Hz}$);
7.43 (1H, triplet, $J = 7.7\text{Hz}$);
7.51 (1H, doublet, $J = 7.7\text{Hz}$);
8.14 (1H, doublet, $J = 7.7\text{Hz}$);
8.72 (1H, broad singlet).

EXAMPLE 189Isopropyl (9-Benzyl-4-isopropyl-1-methylthio-
carbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using isopropyl (4-isopropyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 187, as a starting material, the title compound was obtained in a yield of 83% as an oil.

EXAMPLE 190(9-Benzyl-4-isopropyl-1-methylthiocarbazol-2-yl)-
acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-4-isopropyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 189, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 170 - 171°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

1.49 (6H, doublet, J = 6.8Hz);

1.94 (3H, singlet);

4.00 (1H, sep, J = 6.8Hz);

4.22 (2H, singlet);

6.39 (2H, singlet);

7.0 - 7.1 (2H, multiplet);

7.1 - 7.5 (7H, multiplet);

8.21 (1H, doublet, J = 7.9Hz).

EXAMPLE 1913-(1-Benzylindol-3-yl)propionic Acid

8 ml of a solution of 1.00 g of indol-3-ylpropionic acid in dimethyl formamide were added gradually to 4 ml of a suspension of 460 mg (10.6 mmol) of sodium hydride (55% w/v dispersion in mineral oil) in dimethyl formamide at a temperature of -5°C, and the resulting mixture was stirred for 30 minutes at this temperature. After this time, 1.8 g (10.6 mmol) of benzyl bromide was added to the mixture which was then warmed to room temperature, stirred for 10 min, poured into ice-water, and acidified with a 1 N aqueous solution of hydrogen chloride. The resulting aqueous layer was extracted with methylene chloride, and the extract was dried over anhydrous magnesium sulfate and then the solvent was removed by evaporation under reduced pressure. The residue was recrystallized from a 1 : 1 v/v mixture of ethyl acetate and hexane to yield 1.15 g (79%) of the title compound melting at 121 - 122°C.

EXAMPLE 192(1-Benzylindol-3-yl)thioacetomorpholide

Following procedures and using relative proportions of starting materials similar to those described in Examples 4 and 90, but using 3-acetylindole as a starting material, the title compound was obtained as an oil.

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EXAMPLE 193(1-Benzylindol-3-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using (1-benzylindol-3-yl)thioacetomorpholide, as obtained in Example 192, as a starting material, the title compound was obtained in a yield of 76% as a solid melting at 155-156°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:
 3.82 (2H, singlet);
 5.30 (2H, singlet);
 7.11 - 7.67 (10H, multiplet).

EXAMPLE 194Methyl (1-Benzyl-3-formylindol-6-yl)acetatea) Methyl (1-benzylindol-6-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 1a), but using (1-benzylindol-6-yl)acetic acid, as obtained in Example 67, as a starting material, the title compound was obtained in a yield of 98% as an oil.

b) Methyl (1-benzyl-3-formylindol-6-yl)acetate

18 mg (0.12 mmol) of phosphoryl oxychloride was added gradually to 4 ml of a solution of 25 mg (0.09 mmol) of methyl (1-benzylindol-6-yl)acetate, as obtained in a) above, in dimethyl formamide, at room temperature, and the resulting mixture was stirred for

30 minutes. After this time, an excess of a 2 N aqueous solution of sodium hydroxide was added to the mixture, which was then stirred for 10 minutes. The aqueous layer was extracted with methylene chloride and the extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 25% v/v solution of ethyl acetate in hexane) to yield 23 mg (83%) of the title compound as an oil.

EXAMPLE 195

(1-Benzyl-3-formylindol-6-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl (1-benzyl-3-formylindol-6-yl)acetate, as obtained in Example 194, as a starting material, the title compound was obtained in a yield of 92% as a solid melting at 162-163°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.74 (2H, singlet);

5.33 (2H, singlet);

7.17 - 8.28 (9H, multiplet);

9.96 (1H, singlet).

EXAMPLE 196

Methyl (3-Benzoyl-1-benzylindol-6-yl)acetate

Following a procedure and using relative proportions

of starting materials similar to those described in Example 194 b), but using N,N-dimethylbenzamide as a starting material, the title compound was obtained in a yield of 70% as an oil.

EXAMPLE 197

(3-Benzoyl-1-benzylindol-6-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl (3-benzoyl-1-benzylindol-6-yl)acetate, as obtained in Example 196, as a starting material, the title compound was obtained in a yield of 90% as a solid melting at 195-196°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.75 (2H, singlet);

5.35 (2H, singlet);

7.24 - 8.39 (14H, multiplet).

EXAMPLE 198

Methyl (3-Acetyl-1-benzylindol-6-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 194 b), but using N,N-dimethylacetamide as a starting material, the title compound was obtained in a yield of 75% as an oil.

EXAMPLE 199(3-Acetyl-1-benzylindol-6-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl (3-acetyl-1-benzylindol-6-yl)acetate, as obtained in Example 198, as a starting material, the title compound was obtained in a yield of 88% as a solid melting at 211-212°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

2.50 (3H, singlet);
3.73 (2H, singlet);
5.33 (2H, singlet);
7.14 - 7.35 (7H, multiplet);
7.72 (1H, singlet);
8.34 (1H, doublet, J = 8.0Hz).

EXAMPLE 200(9-Benzyl-1-methylsulfinyl-4-methylcarbazol-2-yl)-
acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-1-methanesulfinyl-4-methylcarbazol-2-yl)acetate, as obtained in Example 215 below, as a starting material, the title compound was obtained in a yield of 96% as a solid melting at 210°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (d₆-DMSO, 270MHz),

δ ppm:

2.74 (3H, singlet);

2.83 (3H, singlet);
3.94 (1H, doublet, J = 16.0Hz);
4.30 (1H, doublet, J = 16.0Hz);
6.18 (2H, singlet);
6.86 (2H, doublet, J = 7.26Hz);
7.01 (1H, singlet);
7.17 - 7.53 (6H, multiplet);
8.20 (1H, doublet, J = 7.88Hz).

EXAMPLE 201

Isopropyl (9-Benzyl-1-methylsulfonyl-4-methyl- carbazol-2-yl)acetate

44 mg (0.25 mmol) of m-chloroperbenzoic acid was added to 6 ml of a solution of 100 mg (0.23 mmol) of isopropyl (9-benzyl-1-methylsulfinyl-4-methylcarbazol-2-yl)acetate, as obtained in Example 215 below, in methylene chloride at room temperature, and the mixture was stirred for 30 minutes. After this time, a saturated aqueous solution of sodium hydrogencarbonate was added to the mixture, the aqueous layer was extracted with methylene chloride, the extract was dried over anhydrous magnesium sulfate and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 50% v/v solution of ethyl acetate in hexane) to yield 90 mg (87%) of the title compound as an amorphous solid.

EXAMPLE 202

(9-Benzyl-1-methylsulfonyl-4-methyl- carbazol-2-yl)acetic Acid

Following a procedure and using relative proportions

of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-1-methanesulfonyl-4-methylcarbazol-2-yl)acetate, as obtained in Example 201, as a starting material, the title compound was obtained in a yield of 95% as a solid melting at 167-168°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.94 (3H, singlet);
3.06 (3H, singlet);
4.31 (2H, singlet);
6.25 (2H, singlet);
6.77 (2H, doublet, $J = 7.7\text{Hz}$);
7.03 (1H, singlet);
7.14 - 7.46 (6H, multiplet);
8.20 (1H, doublet, $J = 7.7\text{Hz}$).

EXAMPLE 203

Isopropyl (4,9-Dimethyl-1-methylsulfinyl-carbazol-2-yl)acetate

a) Isopropyl (4,9-dimethyl-1-methylthiocarbazol-2-yl)-acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using isopropyl (4-methyl-1-methylthiocarbazol-2-yl)acetate and methyl iodide as starting materials, the title compound was obtained in a yield of 80% as an oil.

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b) Isopropyl (4,9-dimethyl-1-methylsulfinyl-carbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 215 below, but using isopropyl (4,9-dimethyl-1-methylthiocarbazol-2-yl)acetate, as obtained in a) above, as a starting material, the title compound was obtained in a yield of 89% as an oil.

EXAMPLE 204

(4,9-Dimethyl-1-methylsulfinylcarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (4,9-dimethyl-1-methylsulfinylcarbazol-2-yl)acetate, as obtained in Example 203, as a starting material, the title compound was obtained in a yield of 84% as a solid melting at 219-220°C.

Nuclear Magnetic Resonance Spectrum (d_6 -DMSO, 270MHz),
δ ppm:

- 2.79 (3H, singlet);
- 3.13 (3H, singlet);
- 3.85 (2H, broad singlet);
- 4.41 (3H, singlet);
- 6.89 (1H, singlet);
- 7.28 (1H, triplet, J = 7.4Hz);
- 7.51 (1H, triplet, J = 7.4Hz);
- 7.63 (1H, doublet, J = 7.8Hz);
- 8.14 (1H, doublet, J = 7.8Hz).

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EXAMPLE 205Isopropyl (1-Benzylthio-4,9-dimethylcarbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 216 below, but using isopropyl (4,9-dimethyl-1-methylsulfinylcarbazol-2-yl)acetate, as obtained in Example 203, and benzyl bromide as starting materials, the title compound was obtained in a yield of 72% as an oil.

EXAMPLE 206(1-Benzylthio-4,9-dimethylcarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (1-benzylthio-4,9-dimethylcarbazol-2-yl)acetate, as obtained in Example 205, as a starting material, the title compound was obtained in a yield of 82% as a solid melting at 187-188°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 2.85 (3H, singlet);
- 3.83 (2H, singlet);
- 3.90 (2H, singlet);
- 4.32 (3H, singlet);
- 6.93 - 7.57 (9H, multiplet);
- 8.16 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 207Isopropyl (4,9-Dimethyl-1-isopropylthio-carbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 216 below, but using isopropyl (4,9-dimethyl-1-methylsulfinylcarbazol-2-yl)acetate, as obtained in Example 203, and isopropyl iodide as starting materials, the title compound was obtained in a yield of 65% as an oil.

EXAMPLE 208(4,9-Dimethyl-1-isopropylthiocarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (4,9-dimethyl-1-isopropylthiocarbazol-2-yl)acetate, as obtained in Example 207, as a starting material, the title compound was obtained in a yield of 90% as a solid melting at 205-206°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.17 (6H, doublet, $J = 6.73\text{Hz}$);
- 2.85 (3H, singlet);
- 3.06 (1H, hepted, $J = 6.7\text{Hz}$);
- 4.23 (2H, broad singlet);
- 4.41 (3H, singlet);
- 7.01 (1H, singlet);
- 7.25 - 7.54 (3H, multiplet);
- 8.15 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 209Isopropyl (4,9-Dimethyl-1-propylthiocarbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 216 below, but using isopropyl (4,9-dimethyl-1-methylsulfinylcarbazol-2-yl)acetate, as obtained in Example 203 and propyl iodide as starting materials, the title compound was obtained in a yield of 69% as an oil.

EXAMPLE 210(4,9-Dimethyl-1-propylthiocarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (4,9-dimethyl-1-propylthiocarbazol-2-yl)acetate, as obtained in Example 209, as a starting material, the title compound was obtained in a yield of 84% as a solid melting at 187-188°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 0.94 (3H, triplet, $J = 7.3\text{Hz}$);
- 1.56 (2H, sextet, $J = 7.4\text{Hz}$);
- 2.66 (2H, triplet, $J = 7.54\text{Hz}$);
- 2.85 (3H, singlet);
- 4.22 (2H, singlet);
- 4.44 (3H, singlet);
- 7.00 (1H, singlet);
- 7.24 - 7.47 (3H, multiplet);
- 8.15 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 211tert-Butyl [4-Methyl-1-methylthio-9-(2-phenethyl)-
carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 2-phenylethyl bromide as starting materials, the title compound was obtained in a yield of 77% as an oil.

EXAMPLE 212[4-Methyl-1-methylthio-9-(2-phenethyl)-
carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [4-methyl-1-methylthio-9-(2-phenethyl)carbazol-2-yl]acetate, as obtained in Example 211, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 181 - 182°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

- 2.29 (3H, singlet);
- 2.86 (3H, singlet);
- 3.04 (2H, triplet, J = 8.1Hz);
- 4.25 (2H, singlet);
- 5.17 (2H, triplet, J = 8.1Hz);
- 7.04 (1H, singlet);
- 7.25 - 7.36 (6H, multiplet);
- 7.51 (2H, doublet, J = 3.3Hz);
- 8.17 (1H, doublet, J = 7.9Hz).

EXAMPLE 213tert-Butyl [4-Methyl-1-methylthio-9-(3-phenylpropyl)-
carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 3-phenylpropyl bromide as starting materials, the title compound was obtained in a yield of 74% as an oil.

EXAMPLE 214[4-Methyl-1-methylthio-9-(3-phenylpropyl)carbazol-2-yl]-
acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [4-methyl-1-methylthio-9-(3-phenylpropyl)carbazol-2-yl]acetate, as obtained in Example 213, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 155 - 156°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.13 (2H, triplet, $J = 7.6\text{Hz}$);

2.2 (3H, singlet);

2.73 (2H, triplet, $J = 7.6\text{Hz}$);

2.84 (3H, singlet);

4.22 (2H, singlet);

4.94 (2H, triplet, $J = 7.6\text{Hz}$);

7.00 (1H, singlet);

7.17 - 7.48 (8H, multiplet);

8.14 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 215Isopropyl (9-Benzyl-4-methyl-1-methylsulfinyl-
carbazol-2-yl)acetate

750 mg of 80% v/v m-chloroperbenzoic acid in water was added gradually to 40 ml of a solution of isopropyl (9-benzyl-1-methylthio-4-methylcarbazol-2-yl)acetate (1.00 g), obtained in a manner similar to that of the title compound of Example 115, in methylene chloride, and the reaction mixture was stirred for 1 hour, with ice-cooling. After this time, the reaction mixture was diluted with an excess of ethyl acetate and washed with a saturated aqueous solution of sodium hydrogen-carbonate. The resulting organic layer was dried over anhydrous sodium sulfate and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 50 - 60% v/v solution of ethyl acetate in hexane) to yield 719 mg of the title compound as a solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.23 (3H, doublet, $J = 6.6\text{Hz}$);
- 1.27 (3H, doublet, $J = 6.6\text{Hz}$);
- 2.51 (3H, singlet);
- 2.91 (3H, singlet);
- 4.18 (1H, doublet, $J = 16.7\text{Hz}$);
- 4.70 (1H, broad singlet);
- 5.03 (1H, multiplet);
- 6.06 (2H, broad singlet);
- 6.90 - 7.50 (9H, multiplet);
- 8.22 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 216Isopropyl (9-Benzyl-4-methyl-1-n-propylthio-carbazol-2-yl)acetate

0.1 ml of anhydrous trifluoroacetic acid was added to 5 ml of a solution of 100 mg isopropyl (9-benzyl-4-methyl-1-methylsulfinylcarbazol-2-yl)acetate, as obtained in Example 215, in methylene chloride, and the reaction mixture was refluxed for 30 minutes. The solvent was then removed by evaporation under reduced pressure and the residue was dissolved in 2 ml of methylene chloride. 0.5 ml of n-propyl iodide, 1 ml of triethylamine and 1 ml of methanol were then all added to the resulting solution at room temperature and the reaction mixture was stirred for 30 minutes. After this time, the reaction mixture was diluted with an excess of ethyl acetate, and washed with a dilute aqueous solution of hydrogen chloride, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, in that order. The resulting organic layer was dried over anhydrous sodium sulfate and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 4 - 6% v/v solution of ethyl acetate in hexane) to yield 86 mg of the title compound as a solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

0.78 (3H, triplet, $J = 7.4\text{Hz}$);

1.22 (6H, doublet, $J = 6.6\text{Hz}$);

1.33 (2H, multiplet);

2.38 (2H, triplet, $J = 7.4\text{Hz}$);

2.89 (3H, singlet);

4.12 (2H, singlet);

5.04 (1H, multiplet);

6.42 (2H, singlet);
6.95 - 7.45 (9H, multiplet);
8.19 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 217

(9-Benzyl-4-methyl-1-n-propylthiocarbazol-2-yl)-
acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using 96 mg of isopropyl (9-benzyl-1-n-propylthio-4-methylcarbazol-2-yl)acetate, as obtained in Example 216, 64 mg of the title compound was obtained as a solid melting at 190-193°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
 δ ppm:

0.81 (3H, triplet, $J = 7.4\text{Hz}$);
1.38 (2H, multiplet);
2.41 (2H, triplet, $J = 7.4\text{Hz}$);
2.94 (3H, singlet);
4.25 (2H, singlet);
6.46 (2H, singlet);
7.00 - 7.50 (9H, multiplet);
8.24 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 218

(9-Benzyl-4-methyl-1-i-propylthiocarbazol-2-yl)-
acetic Acid

Following procedures and using relative proportions of starting materials similar to those described in Examples 216 and 217, but using isopropyl iodide as a

starting material, the title compound was obtained as a solid melting at 207-210°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),
δ ppm:

0.99 (6H, doublet, $J = 6.6\text{Hz}$);
2.89 (3H, singlet);
2.90 (1H, multiplet);
4.23 (2H, singlet);
6.41 (2H, singlet);
7.00 - 7.45 (9H, multiplet);
8.28 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 219

Methyl (9-Benzyl-1-hydroxy-4-methylcarbazol-2-yl)acetate

a) 10-Benzyl-5-methyl-2,3-dihydrofuro[2,3-a]-carbazol-2-one

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using 5-methyl-2,3-dihydrofuro[2,3-a]-carbazol-2-one [obtained as described by Y.Oikawa, M. Tanaka, H. Hirasawa and O. Yonemitsu in Chem. Pharm. Bull., 29, 1606 (1981)], the title compound was obtained as an amorphous solid in a yield of 88%.

b) Methyl (9-benzyl-1-hydroxy-4-methylcarbazol-2-yl)-acetate

0.5 ml of a 1 M methanolic solution of sodium methoxide was added to 5 ml of a methanolic solution of 10-benzyl-5-methyl-2,3-dihydrofuro[2,3-a]carbazol-2-one (80 mg), as obtained in Example 219a) above, with ice-cooling, and the reaction mixture was stirred for 30

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minutes at room temperature. After this time, the reaction mixture was diluted with an excess of an aqueous solution of ammonium chloride and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried over anhydrous sodium sulfate and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 15 - 20% v/v solution of ethyl acetate in hexane) to yield 83 mg of the title compound as a solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.80 (3H, singlet);

3.75 (3H, singlet);

3.82 (2H, singlet);

6.00 (2H, singlet);

6.72 (1H, singlet);

7.10 - 7.50 (8H, multiplet);

8.09 (1H, singlet);

8.16 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 220

Methyl (9-Benzyl-1-methoxy-4-methylcarbazol-2-yl)acetate

120 mg of anhydrous potassium carbonate and 0.14 ml of methyl iodide were added to 4 ml of a solution of 80 mg of methyl (9-benzyl-1-hydroxy-4-methylcarbazol-2-yl)acetate, as obtained in Example 219, in dimethyl formamide, at room temperature, and the reaction mixture was stirred for 1 hour. After this time, the reaction mixture was diluted with an excess of ethyl acetate, and then washed with a saturated aqueous solution of sodium chloride. The resulting organic layer was dried over anhydrous sodium sulfate and then the solvent was

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removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 15 - 20% v/v solution of ethyl acetate in hexane) to yield 84 mg of the title compound as a solid.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.84 (3H, singlet);

3.62 (3H, singlet);

3.71 (3H, singlet);

3.82 (2H, singlet);

5.88 (2H, singlet);

6.91 (1H, singlet);

7.05 - 7.45 (8H, multiplet);

8.17 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 221

(9-Benzyl-1-methoxy-4-methylcarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using 80 mg of methyl (9-benzyl-1-methoxy-4-methylcarbazol-2-yl)acetate, as obtained in Example 220, 61 mg of the title compound was obtained as a solid melting at 200-202°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.84 (3H, singlet);

3.63 (3H, singlet);

3.85 (2H, singlet);

5.87 (2H, singlet);

6.91 (1H, singlet);

7.05 - 7.45 (8H, multiplet);

8.17 (1H, doublet, $J = 7.8\text{Hz}$).

EXAMPLE 222

[9-(4-Methoxycarbonylbenzyl)-1-methylcarbazol-2-yl]-
acetic Acid

- a) Methyl [9-(4-methoxycarbonylbenzyl)-1-methyl-
carbazol-2-yl]-acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using methyl (1-methylcarbazol-2-yl)-acetate and 4-methoxycarbonylbenzyl bromide as starting materials, the title compound was obtained as an oil.

- b) [9-(4-Methoxycarbonylbenzyl)-1-methylcarbazol-2-yl]-
acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl [9-(4-methoxycarbonylbenzyl)-1-methylcarbazol-2-yl]-acetate, as obtained in a) above, as a starting material, the title compound was obtained as a solid melting at 200-202°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

2.50 (3H, singlet);
3.83 (2H, singlet);
3.88 (3H, singlet);
5.77 (2H, singlet);
7.10 - 7.45 (7H, multiplet);
7.98 (2H, doublet, J = 8.0Hz);
8.10 (1H, doublet, J = 8.2Hz).

EXAMPLE 223[9-(4-Carboxylbenzyl)-1-methylcarbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using [9-(4-methoxycarbonylbenzyl)-1-methylcarbazol-2-yl]acetic acid, as obtained in Example 222, as a starting material, the title compound was obtained as a solid melting at 220-225°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 + tetradeuterated methanol, 270MHz), δ ppm:

- 2.52 (3H, singlet);
- 3.82 (2H, singlet);
- 5.80 (2H, singlet);
- 7.10 - 7.50 (7H, multiplet);
- 7.93 (2H, doublet, $J = 8.0\text{Hz}$);
- 8.10 (1H, doublet, $J = 8.2\text{Hz}$).

EXAMPLE 224[9-(4-Carbamoylbenzyl)-1-methylcarbazol-2-yl]acetic Acid

[9-(4-Methoxycarbonylbenzyl)-1-methylcarbazol-2-yl]-acetic acid, as obtained in Example 222, was treated with methanolic ammonia at room temperature to afford the title compound as a solid melting at 255-260°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 + tetradeuterated methanol, 270MHz), δ ppm:

- 2.50 (3H, singlet);
- 3.86 (2H, singlet);
- 5.78 (2H, singlet);

7.10 - 7.40 (7H, multiplet);
7.92 (2H, doublet, $J = 8.0\text{Hz}$);
8.06 (1H, doublet, $J = 8.2\text{Hz}$).

EXAMPLE 225

Methyl (1-Benzylindol-6-yl)acrylate

Following procedures and using relative proportions of starting materials similar to those described in Examples 35 and 4, but using indol-6-ylcarbaldehyde, the title compound was obtained as an oily material.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

3.79 (3H, singlet);
5.33 (2H, singlet);
6.40 (1H, doublet, $J = 18.0\text{Hz}$);
6.58 (1H, doublet, $J = 3.2\text{Hz}$);
7.10 - 7.40 (8H, multiplet);
7.61 (1H, doublet, $J = 8.0\text{Hz}$);
7.88 (1H, doublet, $J = 18.0\text{Hz}$).

EXAMPLE 226

(1-Benzylindol-6-yl)acrylic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using methyl (1-benzylindol-6-yl)-acrylate, as obtained in Example 225, the title compound was obtained as a solid melting at 202-204°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

5.33 (2H, singlet);
6.40 (1H, doublet, $J = 18.0\text{Hz}$);
6.57 (1H, doublet, $J = 3.2\text{Hz}$);
7.10 - 7.50 (9H, multiplet);
7.86 (1H, doublet, $J = 18.0\text{Hz}$).

EXAMPLE 227

(1-Benzylindol-6-yl)propionic Acid

Following procedures and using relative proportions of starting materials similar to those described in Examples 36 and 26, but using methyl (1-benzylindol-6-yl)acrylate, as obtained in Example 225, the title compound was obtained as a solid melting at 104-106°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.68 (2H, triplet, $J = 8.0\text{Hz}$);
3.02 (2H, triplet, $J = 8.0\text{Hz}$);
5.31 (2H, singlet);
6.50 (2H, doublet, $J = 3.2\text{Hz}$);
6.89 (1H, doublet, $J = 8.4\text{Hz}$);
7.10 - 7.40 (7H, multiplet);
7.58 (1H, doublet, $J = 8.4\text{Hz}$).

EXAMPLE 228

N-(9-Benzyl-4-methyl-1-methylthiocarbazol-2-ylacetyl)-methylsulfonamide

74.6 mg (0.26 mmol) of carbonyldiimidazole was added to 1 ml of a solution of 50 mg (0.13 mmol) of (9-benzyl-4-methyl-1-methylthiocarbazol-2-yl)acetic acid, as obtained in Example 14, in tetrahydrofuran, and

the reaction mixture was stirred for 1 hour at room temperature. After this time, 43.8 mg (0.26 mmol) of methanesulfonamide and 70.0 mg (0.26 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene were added to the mixture which was first stirred overnight at room temperature and then refluxed for 2 hours. After this time, an excess of water was added to the mixture, and the resulting aqueous layer was extracted with ethyl acetate. The extracted organic layer was first washed with water and then with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and the solvent was then removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 50% v/v solution of ethyl acetate in hexane) to yield 48 mg (80%) of the title compound.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.93 (3H, singlet);
- 2.91 (3H, singlet);
- 3.22 (3H, singlet);
- 4.10 (2H, singlet);
- 6.35 (2H, singlet);
- 6.97 - 7.53 (9H, multiplet);
- 8.00 (1H, singlet);
- 8.22 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 229

{9-[2-(3-Chlorophenyl)ethyl]-4-methyl-1-methylthio-carbazol-2-yl}acetic Acid

- a) tert-Butyl {9-[2-(3-Chlorophenyl)ethyl]-4-methyl-1-methylthio-carbazol-2-yl}acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 2-(3-chlorophenyl)ethyl bromide as starting materials, the title compound was obtained in a yield of 73% as an oil.

- b) {9-[2-(3-Chlorophenyl)ethyl]-4-methyl-1-methylthio-carbazol-2-yl}acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl {9-[2-(3-chlorophenyl)-ethyl]-4-methyl-1-methylthiocarbazol-2-yl}acetate, as obtained in a), as a starting material, the title compound was obtained in a quantitative yield, as a solid melting 171-178°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 2.29 (3H, singlet);
- 2.86 (3H, singlet);
- 2.95 - 3.05 (2H, multiplet);
- 4.24 (2H, singlet);
- 5.10 - 5.20 (2H, multiplet);
- 7.05 (1H, singlet);
- 7.13 - 7.53 (7H, multiplet);
- 8.17 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 230(1-Methylthio-4-trifluoromethylcarbazol-2-yl)acetic Acida) Diethyl 1-(indol-3-yl)-2,2,2-trifluoroethylmalonate

400 mg (17.4 mmol) of sodium was added to 10 ml of a solution of 2.23 g (13.9 mmol) of diethyl malonate in toluene under a stream of nitrogen gas, and the reaction mixture was refluxed for 2 hours. After this time, the reaction mixture was cooled to room temperature, and 6 ml of a toluene solution of 1.00 g (4.6 mmol) of 1-(indol-3-yl)-2,2,2-trifluoroethanol were added. The resulting mixture was then refluxed for 30 minutes. After this time, the mixture was added to 100 ml of ethanol, acidified with a dilute aqueous solution of hydrogen chloride, and the solvent was removed by evaporation under reduced pressure. The resulting aqueous layer was extracted with ethyl acetate and the extracted organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and the solvent removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 20% v/v solution of ethyl acetate in hexane) to yield 1.49 g (91%) of the title compound.

b) 3-(Indol-3-yl)-4,4,4-trifluorobutyric acid

Following procedures and using relative proportions of starting materials similar to those described in Examples 109 and 110, but using diethyl 1-(indol-3-yl)-2,2,2-trifluoroethylmalonate, as obtained in a) above, as a starting material, the title compound was obtained as an amorphous solid.

c) Isopropyl (1-methylthio-4-trifluoromethylcarbazol-2-yl)acetate

Following procedures and using relative proportions of starting materials similar to those described in Examples 1 and 2, but using 3-(indol-3-yl)-4,4,4-trifluorobutyric acid, as obtained in b) above, as a starting material, the title compound was obtained as an oil.

d) (1-Methylthio-4-trifluoromethylcarbazol-2-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (1-methylthio-4-trifluoromethylcarbazol-2-yl)acetate, as obtained in c) above, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 115-120°C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270MHz),

δ ppm:

2.39 (3H, singlet);

4.22 (2H, singlet);

7.28 - 7.56 (4H, multiplet);

8.28 (1H, doublet, J = 8.2 Hz);

8.88 (1H, singlet);

EXAMPLE 231(9-Benzyl-1-methylthio-4-trifluoromethylcarbazol-2-yl)
acetic Acid

- a) Isopropyl (9-benzyl-1-methylthio-4-trifluoromethyl-
carbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using isopropyl (1-methylthio-4-trifluoromethylcarbazol-2-yl)acetate, as obtained in Example 230 c), as starting material, the title compound was obtained in a yield of 88% as an oil.

- b) (9-Benzyl-1-methylthio-4-trifluoromethylcarbazol-2-
yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-1-methylthio-4-trifluoromethylcarbazol-2-yl)acetate, as obtained in a) above, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 166-167°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

- 1.97 (3H, singlet);
4.24 (2H, singlet);
6.40 (2H, singlet);
7.03 - 7.56 (9H, multiplet);
8.36 (1H, doublet, $J = 8.1\text{Hz}$).

EXAMPLE 232(4-Methylthiocarbazol-3-yl)acetic Acida) Isopropyl (4-methylthiocarbazol-3-yl)acetate

Following procedures and using relative proportions of starting materials similar to those described in Examples 1a), 34, 35, 36, 1b), 1c), 1d) and 2, but using indol-2-ylcarboxylic acid as starting material, the title compound was obtained as an oil.

b) (4-Methylthiocarbazol-3-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (4-methylthiocarbazol-3-yl)acetate, as obtained in a) above, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 200 - 210°C (with decomposition).

Nuclear Magnetic Resonance Spectrum (CDCl_3 + tetradeuterated methanol, 270MHz), δ ppm:

2.40 (3H, singlet);
4.18 (2H, singlet);
7.20 - 7.50 (5H, multiplet);
8.87 (1H, doublet, $J = 8.0\text{Hz}$).

EXAMPLE 233(9-Benzyl-4-methylthiocarbazol-3-yl)acetic Acida) Isopropyl (9-benzyl-4-methylthiocarbazol-3-yl)acetate

Following a procedure and using relative proportions

of starting materials similar to those described in Example 4, but using isopropyl (4-methylthiocarbazol-3-yl)acetate, as obtained in Example 232 a), as a starting material, the title compound was obtained in a yield of 91% as an oil.

b) (9-Benzyl-4-methylthiocarbazol-3-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-4-methylthiocarbazol-3-yl)acetate, as obtained in a) above, as a starting material, the title compound was obtained in a quantitative yield as a solid melting 181-189°C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270MHz),

δ ppm:

2.42 (3H, singlet);

4.22 (2H, singlet);

5.51 (2H, singlet);

7.10 - 7.50 (10H, multiplet);

8.94 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 234

(9-Benzyl-1-isopropylthiocarbazol-4-methyl-2-yl)methyl-1H-tetrazole

Following procedures and using relative proportions of starting materials similar to those described in Examples 75, 76 and 77, but using (9-benzyl-1-isopropylthio-4-methylcarbazol-2-yl)acetic acid, as obtained in Example 218, as a starting material, the title compound was obtained as a solid melting at 231 - 232°C.

Nuclear Magnetic Resonance Spectrum (tetradeuterated methanol, 270MHz), δ ppm:

- 1.03 (6H, doublet, $J = 6.7\text{Hz}$);
- 2.94 (4H, multiplet);
- 4.83 (2H, broad singlet);
- 6.43 (2H, broad singlet);
- 6.98 - 7.47 (9H, multiplet);
- 8.21 (1H, doublet, $J = 7.9\text{Hz}$).

EXAMPLE 235

(9-Benzyl-4-isopropyl-1-isopropylthiocarbazol-2-yl)
acetic Acid

- a) Isopropyl (9-benzyl-4-isopropyl-1-isopropylthio-
carbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 216, but using isopropyl (4-isopropyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 189, as a starting material, the title compound was obtained in a yield of 77% as an oil.

- b) (9-Benzyl-4-isopropyl-1-isopropylthiocarbazol-2-yl)
acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-4-isopropyl-1-isopropylthiocarbazol-2-yl)acetate, as obtained in a) above, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at $217 - 218^{\circ}\text{C}$.

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Nuclear Magnetic Resonance Spectrum (CDCl_3 +
tetradeuterated methanol in a ratio of 20 : 1 v/v,
270MHz), δ ppm:

0.98 (6H, doublet, $J = 6.8\text{Hz}$)
1.50 (6H, doublet, $J = 6.8\text{Hz}$);
2.80 (1H, quintuplet, $J = 6.8\text{Hz}$);
3.99 (1H, quintuplet, $J = 6.8\text{Hz}$);
4.23 (2H, singlet);
6.42 (2H, singlet);
7.04 - 7.42 (9H, multiplet);
8.20 (1H, doublet, $J = 7.9\text{Hz}$).

The compounds of the present invention may be administered in any suitable fashion for the desired treatment. For example, the compounds of the present invention can be administered orally in the form of tablets, capsules, granules, powders or syrups, or parenterally by intravenous injection, or as suppositories or the like. These pharmaceutical formulations can be prepared by mixing the compounds of the present invention with one or more adjuvants, such as excipients (e.g. organic excipients including sugar derivatives, such as lactose, sucrose, glucose, mannitol or sorbitol; starch derivatives, such as corn starch, mashed potato, α -starch, dextrine or carboxymethyl starch; cellulose derivatives, such as crystalline cellulose, low hydroxypropyl-substituted cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, carboxymethyl cellulose calcium or internally bridged carboxymethyl cellulose sodium; gum arabic; dextran; and

Pullulan; inorganic excipients including silicates, such as light silicic acid anhydride, synthetic aluminium silicate or magnesium meta-silicic acid aluminate; phosphates, such as calcium phosphate; carbonates, such as calcium carbonate; and sulphates, such as calcium sulphate); lubricants (e.g. metal stearates, such as stearic acid, calcium stearate or magnesium stearate; talc; colloidal silica; waxes, such as beeswax or spermaceti; boric acid; adipic acid; sulphates, such as sodium sulphate; glycol; fumaric acid; sodium benzoate; DL-leucine; sodium salts of aliphatic acids; lauryl sulphates, such as sodium laurylsulphate or magnesium laurylsulphate; silicates, such as silicic acid anhydride or silicic acid hydrate; and the foregoing starch derivatives); binders (e.g. polyvinyl pyrrolidone, Macrogol; and similar compounds to the excipients described above); disintegrating agents (e.g. similar compounds to the excipients described above; and chemically modified starch-celluloses, such as Crosscarmellose sodium, sodium carboxymethyl starch or bridged polyvinyl pyrrolidone); stabilisers (e.g. p-hydroxybenzoates, such as methylparaben or propylparaben; alcohols, such as chlorobutanol, benzyl alcohol or phenylethyl alcohol; benzalkonium chloride; phenols, such as phenol or cresol; thimerosal; dehydroacetic acid; and sorbic acid); corrigents (e.g. sweeteners, vinegar or perfums, such as those conventionally used); diluents and the like.

The compounds of the present invention may also be administered by any other suitable route, such as: parenterally, intravenously, eye-drops, suppositories, dermal patch and sustained release formulations, using any suitable excipients, preservatives, flavourings, colourings and other ingredients as appropriate and/or desired.

The dose varies depending upon the condition and age of the patient and upon the route and type of administration but, for example, the compounds of the present invention can be administered orally in a daily dose of from 0.01 to 1000 mg/kg body weight (preferably 0.05 to 200 mg/kg body weight), either as a single dose or as divided doses.

BIOLOGICAL ACTIVITY

The compounds of the present invention may be assayed for allosteric activity at m1 muscarinic receptors as described below, although the assays we describe are not necessarily exhaustive, and other assays may be employed, as desired, to establish allosterism.

It will be understood that the present invention also envisages any of the accompanying assays, as described below, as well as any compounds, and the use of any compounds, which exhibit an allosteric effect by any one or more of such assays.

In the following assays, it is necessary, or at least desirable, to use a cell line which expresses only one type of muscarinic receptor, such as m1, and which does not exhibit a high level of acetylcholinesterase activity.

A suitable cell line is CHO (Chinese Hamster Ovary), which are readily engineered to express only one receptor sub-type.

Preparation of CHO cell membranes

To obtain the large amount of cell membranes required, plates of 530 cm² culture area were used.

CHO cells which express m1, m2, m3 and m4 receptors were grown separately in MEM alpha medium containing 10% newborn calf serum and antibiotics. When cells reached confluence, they were washed twice with 10 ml of 20 mM HEPES containing 10 mM EDTA (pH 7.4), scraped into the same buffer and homogenized using a Polytron (trademark) homogenizer (setting 5-6 for 5 sec x 2). Membrane pellets were obtained by centrifugation (40000xg, 10 min, 4°C) and resuspended in 20 mM HEPES - 0.1 mM EDTA (pH 7.4). Centrifugation and resuspension were repeated twice to wash the cell membranes. After measurement of membrane protein, the membranes (1 or 2 mg protein/ml) were stored at -70°C.

ACh inhibition of ^3H -NMS binding

While the direct assay measures ACh (=acetylcholine) binding only to the high affinity state, the indirect assay measures effects only at the low affinity state. This is achieved by including 0.2 mM GTP in the assay. In this assay a fixed concentration of ^3H -NMS (roughly the K_d value) is incubated in the absence and presence of a fixed concentration of ACh (at about the IC_{50} value) and the effects of three concentrations of test agent are measured, again in the absence and presence of ACh.

Calculating the effects on ^3H -NMS binding alone is as follows: binding in the presence of the agent is expressed as a percentage of binding in its absence and, if the effect is inhibitory, an IC_{50} is estimated graphically. The assay also contains a single high concentration of ^3H -NMS (4 nM, about 30 times the K_d) which provides an estimate of B_{max} (i.e. maximum binding). Assuming that the agent acts only allosterically, and to modify only the affinity of

$^3\text{H-NMS}$ with no effect on B_{max} , the affinity of $^3\text{H-NMS}$ in the presence of the agent can be estimated and hence the allosterism.

Expressing the effect on cold ACh binding will be explained with reference to Figures 1a, b and c. These figures show theoretical data and the effects of the transformations described below. In figures 1a and 1b $^3\text{H-NMS}$ and cold ACh are present at their K_d concentrations; in figure 1a the agent has a negative allosteric effect on $^3\text{H-NMS}$, while in figure 1b it has a positive allosteric effect on $^3\text{H-NMS}$. The left panels show the amount of $^3\text{H-NMS}$ specifically bound in the assay. If the affinity of ACh is reduced by the test agent, as shown in the top panels of figures 1a and 1b, the inhibition by ACh will decrease, but the counts recovered will also depend on the effect of the agent on $^3\text{H-NMS}$ binding alone. To calculate the effect on ACh binding the inhibitory effect of ACh is first calculated as a percent of its own control in the absence of ACh. Next it is assumed that fractional inhibition is the same as fractional occupancy, and inhibition in the presence of agent is expressed as a percentage of inhibition in the absence of agent. The effects of these transformations are shown in the centre panels. Expressing inhibition by ACh in the presence of agent as a percentage of inhibition in the absence of agent allows the effect of the agent on cold ACh binding to be seen on the same scale as the effect on $^3\text{H-NMS}$ and $^3\text{H-ACh}$ binding and is generally preferred.

If the concentration of $^3\text{H-NMS}$ used in the indirect assay is around the K_d value or less, the transformation described above provides a qualitative and semi-quantitative measure of the agent's effect. If a higher concentration of $^3\text{H-NMS}$ is used, or if the agent has a positive allosteric effect on $^3\text{H-NMS}$, then

the results of this transformation may be misleading. This is demonstrated in figure 1c, where a high $^3\text{H-NMS}$ concentration and positive allosterism on $^3\text{H-NMS}$ make the agent have an inhibitory effect on ACh binding expressed as percentage of control inhibition, even though the agent actually has a positive effect on ACh affinity. This problem is reduced or eliminated by estimating the affinity of ACh and hence the allosterism. It is assumed that ACh binds to a single affinity state i.e. that its inhibition curve has a slope of 1, and so an IC_{50} is calculated from the percentage inhibition of control binding. This value is used with the estimate of $^3\text{H-NMS}$ affinity described above to calculate the ACh affinity. The allosterism of the agent on both $^3\text{H-NMS}$ and cold ACh is shown in the right panels of figures 1a-1c.

Estimation of affinity constants (pKi)

If the three concentrations of agent used in the assay are appropriate, and the agent has an inhibitory effect, it is possible to estimate the apparent affinity (pKi) of the agent in competition with $^3\text{H-NMS}$ and hot and cold ACh. The allosterism transformation shows the potency of the agent independently of the concentrations of $^3\text{H-NMS}$ and cold ACh in the assay and, in the case of cold ACh, independently of effects on $^3\text{H-NMS}$ binding, but involves some assumptions. We prefer to read the data off the graph as pIC_{50} values and then convert them to pKi values using correction factors derived from the theory of competitive antagonism - this correction also works with negative allosteric agents [Ehlert, Mol. Pharmacol. 33, 187, (1988)]. In order to allow for the influence of $^3\text{H-NMS}$ concentration, the pIC_{50} values with $^3\text{H-NMS}$ are converted to pKi values using the Cheng-Prussoff equation

$$K_i = \text{IC}_{50} / ([^3\text{H-NMS}] / K_d + 1)$$

The equivalent correction factor in the presence of cold ACh is

$$K_i = IC_{50} / ([^3H-NMS] / K_d + [ACh] / K_a + 1)$$

It is often not possible to read pIC_{50} values off the graph because 50% inhibition is not reached (a frequent occurrence with weak agents) but 50% inhibition may have been obtained with the allosterism measure, in which case this value is read off the graph as the pK_i value, without further transformation.

The use of non-linear regression analysis to estimate pK_i values and weak allosterism

While the estimation of pK_i values from visual inspection of graphs is quick and usually adequate, there are two circumstances which justify the use of more time-consuming curve-fitting procedures. Firstly, there may be a clear and quantifiable inhibitory trend in the data even though 50% inhibition was not attained. Secondly, aspects of the data may suggest that the agent is acting as a weakly allosteric agent. If the agent is a strong allosteric, or competitive, inhibitor then it should cause maximally 100% inhibition and its pK_i against ^3H-NMS should be approximately equal to its pK_i against hot or cold ACh. A weak allosteric agent, however, will maximally inhibit less than 100% of the binding, and pK_i values simply read off the graph will underestimate its 'true' pK_i . It is necessary, given the paucity of data under normal test conditions, to constrain the slope of the inhibition curve to unity, and the fitted estimates are only accepted if their standard errors are suitably low (about 0.3 log units for pIC_{50} and 15% of the estimate for maximal inhibition). If % inhibition data are fitted then the correction factor is applied to convert pIC_{50} to pK_i values.

Procedure

Membranes (10 μ g of protein) are incubated in 1.12 ml (3 H-NMS) or 0.25 ml (3 H-ACh) of buffer containing 20mM HEPES + 100 mM NaCl + 10 mM MgCl₂ (+0.2 mM GTP in 3 H-NMS assays), pH 7.4, at 30°C for two hours. The bound radioligand is collected by filtration through Whatman GF/B glass-fibre filters soaked in 0.1% polyethylenimine using a 30-place Brandel cell harvester, and the radioactivity measured with liquid scintillation counting. Nonspecific binding is measured in the presence of 1 μ M QNB.

Design and analysis

The 3 H-NMS assay contains 0.2 mM GTP and uses 3 H-NMS concentrations of about 4 and 0.15 nM. The fixed ACh concentration is 30 μ M. Total and nonspecific binding are measured with 4 nM 3 H-NMS to provide an estimate of B_{max} . Using 0.15 nM 3 H-NMS, binding in the absence and presence of ACh is measured alone and in the presence of three concentrations of each of four agents, and nonspecific binding is measured with QNB alone. Each point is measured in duplicate (quadruplicate for 0.15 nM 3 H-NMS alone).

The data are analyzed as described above, and graphs produced, using the Minitab program. Where possible, IC_{50} values are estimated visually from the graphs.

Results for some of the compounds of the present invention are presented in the Activity Table below. Each compound was tested at 3 μ g/ml.

ACTIVITY TABLE

Compound of Example	Effect on ACh Binding
<hr/>	
5	2.62
7	3.55
8	3.46
14	3.89
15	2.42
17	2.50
23	2.72
37	2.09
46	2.21
61	2.11
77	3.69
83	2.08
84	3.30
91	2.76
97	4.97
116	3.99
132	2.68
134	3.40
136	2.36
141	3.81
143	5.36
145	5.27
149	6.49
152	2.02
165	2.24
172	2.59
176	2.08
180	5.02
182	2.57
190	4.78

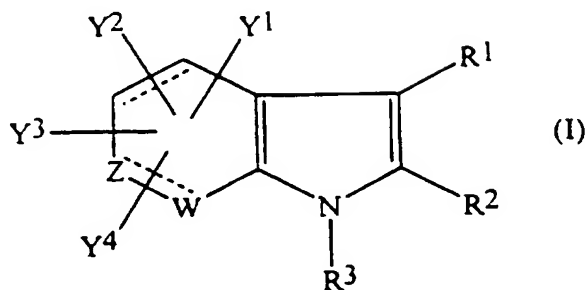
200	3.59
202	2.66
206	2.13
210	2.03
212	4.93
214	4.34
217	3.99
218	4.91
229	5.79
231	3.78
233	2.26
235	2.82

M&C FOLIO: 72553/FP-9509

WANGDOC: 1123D

What is claimed is:

1. A compound of formula (I):



wherein:

Z represents a methylene group, a methine group, a group of formula $>NH$ or a group of formula $=N-$, and W represents a methylene group, a methine group, a sulfur atom or a group of formula $>S-(O)_v$, where v is 1 or 2, provided that Z does not represent a group of formula $>NH$ when W represents a group of formula $>S-(O)_v$;

each \dots represents a single bond or a double bond, provided that when W represents a sulfur atom or a group of formula $>S-(O)_v$, then the \dots bond between W and Z represents a single bond;

at least one of Y^1 , Y^2 , Y^3 and Y^4 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a group of formula $-(A)_p-B^1-T^1$,

wherein A represents an oxygen atom or a sulfur atom, T^1 represents a carboxyl group, a thiocarboxy group, a dithiocarboxy group, a protected carboxyl group, a protected thiocarboxy group, a protected

dithiocarboxy group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group, B^1 represents a direct bond, an alkylene group which has from 1 to 4 carbon atoms, or an alkylene group which has from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from substituents α , defined below, and p is 0 or 1;

any members of the group Y^1 , Y^2 , Y^3 and Y^4 which are not as defined above may be the same or different and each represents a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, a thiol group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms and which is substituted with a keto group or at least one substituent γ defined below, an alkoxy group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkylsulfinyl group having from 1 to 6 carbon atoms, an alkylsulfonyl group having from 1 to 6 carbon atoms, an aryl group, an aralkyloxy group, an aralkylthio group,

and

Y^1 , together with Y^2 , may represent a lactone group or a keto group;

one of R^1 and R^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkanoyl group having from 1 to 6 carbon atoms, an aryl group, an arylcarbonyl group having from 7 to 15 carbon atoms, an aralkyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_q-B^2-T^2$,

wherein T^2 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a

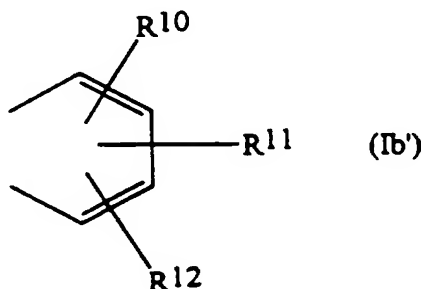
protected sulfonamide group or a tetrazolyl group,
 B^2 represents an alkylene group which has from 1
 to 6 carbon atoms or an alkylene group which has
 from 1

to 6 carbon atoms and which has one or more substituents
 selected from amino groups, protected amino groups,
 hydroxyl groups and protected hydroxyl groups, and
 q is 0 or 1;

the other of R^1 and R^2 representing a hydrogen atom,
 an alkyl group having from 1 to 6 carbon atoms, an aryl
 group or an aralkyl group,

or

R^1 and R^2 together represent a group of formula
 (Ib'):



[in which R^{10} , R^{11} and R^{12} are the same or
 different and each represents a hydrogen atom, a
 hydroxy group, a halogen atom, a haloalkyl group, an
 alkyl group having from 1 to 6 carbon atoms, an
 alkyl group having from 1 to 6 carbon atoms and
 having at least one substituent γ defined below,
 an alkoxy group having from 1 to 6 carbon atoms, an
 alkylthio group having from 1 to 6 carbon atoms, an
 alkylsulfinyl group having from 1 to 6 carbon atoms
 or an alkylsulfonyl group having from 1 to 6 carbon
 atoms];

R^3 represents a hydrogen atom or an amino protecting group;

said aryl groups being carbocyclic aromatic groups having from 6 to 14 carbon atoms, which may be unsubstituted or substituted with at least one substituent selected from substituents β defined below;

the alkyl parts of said aralkyl groups having from 1 to 3 carbon atoms, the aryl part being as defined above;

substituents α

hydroxyl groups, alkyl groups having from 1 to 6 carbon atoms, alkoxy groups having from 1 to 6 carbon atoms, alkylthio groups having from 1 to 6 carbon atoms, aryl groups as defined above and aralkyl groups as defined above;

substituents β

halogen atoms, nitro groups, hydroxyl groups, amino groups, protected amino groups, alkyl groups having from 1 to 6 carbon atoms, alkoxycarbonyl groups having from 2 to 7 carbon atoms, carboxyl groups, carboxamide groups and aralkoxy groups wherein the aralkyl part is as defined above;

substituents γ

hydroxyl groups, halogen atoms and aryl groups as defined above;

and pharmaceutically acceptable salts and esters thereof.

2. The compound of claim 1, wherein W is a methine group, a methylene group or a sulfur atom.

3. The compound of claim 1, wherein W is a methine group.

4. The compound of claim 1, wherein ... represents a double bond.
5. The compound of claim 1, wherein at least one of Y^1 , Y^2 , Y^3 and Y^4 represents a carboxyl group, a sulfonamide group or a group of formula $-(A)_p-B^1-T^1$.
6. The compound of claim 1, wherein at least one of Y^1 , Y^2 , Y^3 and Y^4 represents a group of formula $-(A)_p-B^1-T^1$.
7. The compound of claim 1, wherein A represents an oxygen atom.
8. The compound of claim 1, wherein T^1 represents a carboxyl group, a thiocarboxy group, a dithiocarboxy group or a tetrazolyl group.
9. The compound of claim 1, wherein T^1 represents a carboxyl group or a tetrazolyl group.
10. The compound of claim 1, wherein B^1 represents an alkylene group which has from 1 to 4 carbon atoms or an alkylene group which has from 1 to 4 carbon atoms and which is substituted by at least one aralkyl group.
11. The compound of claim 10, wherein said alkylene group has 1 or 2 carbon atoms.
12. The compound of claim 1, wherein p is 0.
13. The compound of claim 1, wherein any members of the group Y^1 , Y^2 , Y^3 and Y^4 which are not defined above are the same or different and each represents a hydrogen atom, a hydroxyl group, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1

to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkylsulfinyl group having from 1 to 6 carbon atoms, an alkylsulfonyl group having from 1 to 6 carbon atoms, an aralkyloxy group, an aralkylthio group,

and

Y^1 , together with Y^2 , may represent a keto group.

14. The compound of claim 1, wherein any members of the group Y^1 , Y^2 , Y^3 and Y^4 which are not defined above are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms or an alkylthio group having from 1 to 6 carbon atoms.

15. The compound of claim 1, wherein one of R^1 and R^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group.

16. The compound of claim 1, wherein one of R^1 and R^2 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.

17. The compound of claim 16, wherein the other of R^1 and R^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group.

18. The compound of claim 16, wherein the other of R^1 and R^2 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.

19. The compound of claim 1, wherein R^1 and R^2 together represent said group of formula (Ia).

20. The compound of claim 19, wherein R^{10} , R^{11} and R^{12} are the same or different and each represents a

hydrogen atom, a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms or an alkylthio group having from 1 to 6 carbon atoms.

21. The compound of claim 1, wherein R^3 represents an aralkyl group.

22. The compound of claim 1, wherein R^3 represents a benzyl or phenethyl group.

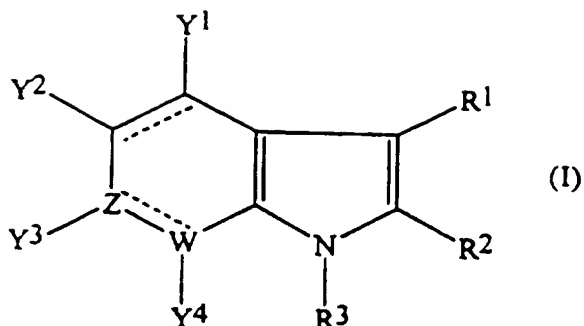
23. The compound of claim 1, wherein R^3 represents a benzyl or phenethyl group substituted with at least one substituent selected from the group consisting of halogen atoms and nitro groups.

24. The compound of claim 1, wherein R^3 represents a benzyl group.

25. The compound of claim 1, wherein said aryl groups are selected from carbocyclic aromatic groups having from 6 to 10 carbon atoms and carbocyclic aromatic groups having from 6 to 10 carbon atoms and which have at least one substituent selected from substituents β .

26. The compound of claim 1, wherein said aralkyl groups are unsubstituted or substituted with at least one substituent selected from the group consisting of halogen atoms and nitro groups.

27. A compound of formula (I):



wherein W is -S-, -C--- or is a group of Formula $>S-(O)_v$ where v is 1 or 2;

Z is -C---, >N- or =N-;

the dotted lines individually indicate that the bond to which they are adjacent is a single or a double bond;

Y^1 represents a hydrogen atom, a thiol group, a hydroxy group, a cyano group, an acetyl group, an alkyl group having from 1 to 6 carbon atoms, a perhaloalkyl group having 1 or 2 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkyl group having 1 or 2 substituents selected from substituents g below, an aralkyl group or an aralkyl group substituted with one or more substituents selected from substituents f below;

Y^2 and Y^3 are the same or different, and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a carboxyl group, an alkylcarbonyl group having from 1 to 6 carbon atoms, a hydroxyl group, an alkoxy group having from 1 to 6 carbon atoms, an alkoxy group substituted with one or more substituents selected from substituents g below, a cyano group, a carbamoyl group, a group of Formula $-CONR^{30}R^{31}$, wherein R^{30} and R^{31} are as defined below, an

alkylthio group having from 1 to 6 carbon atoms, an alkylthio group substituted with one or more substituents selected from substituents f below or an alkyl group substituted with one or more substituents selected from substituents h below;

Y^4 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms, an aryloxy group, an alkylthio group having from 1 to 6 carbon atoms, a hydroxyl group, a thiol group, a methylsulfonyl group, a methylsulfinyl or an arylthio group;

R^3 represents an alkylcarbonyl group having from 1 to 6 carbon atoms, a hydrogen atom, a methylsulfonyl group, an alkyl group having from 1 to 6 carbon atoms, a benzoyl group, a benzoyl group substituted with one or more substituents selected from substituents f below, an aryl group, an aryl group substituted with one or more substituents selected from substituents f below, an alkyl group having from 1 to 6 carbon atoms and substituted with one or more substituents selected from substituents h below, an aralkyl group wherein the alkyl part has from 1 to 6 carbon atoms or an aralkyl group wherein the alkyl group has from 1 to 6 carbon atoms and the aryl part is substituted with one or more substituents selected from substituents f below;

R^2 and R^1 are the same or different, and each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms,

or

together, R^1 and R^2 form a phenyl group fused at the bond joining R^2 and R^1 , said phenyl group optionally being substituted with one or more of substituents f below, one of the ring carbon atoms optionally being replaced by a nitrogen atom;

said aryl groups and aryl parts of said aralkyl groups being carbocyclic aromatic groups having from 6 to 14 carbon atoms, which may be unsubstituted or substituted with at least one substituent selected from substituents f defined below;

substituents f

aryloxy groups, nitro groups, halogen atoms, carbamoyl groups, hydroxy groups, alkoxy groups having 1 to 6 carbon atoms, tetrazolyl groups, carboxyl groups and aryl groups;

substituents g

aryl groups, carboxyl groups, cyano groups, hydroxy groups, halogen atoms, thiol groups, amino groups and mono- or di- alkyl amino groups wherein said alkyl groups each have from 1 to 6 carbon atoms, groups of formula $\text{CONR}^{30}\text{R}^{31}$ wherein R^{30} and R^{31} each represents an alkyl group having from 1 to 6 carbon atoms or, together with the nitrogen to which they are joined form a cyclic or heterocyclic group, or a group of formula $\text{CSNR}^{30}\text{R}^{31}$ where R^{30} and R^{31} are as defined above;

substituents h

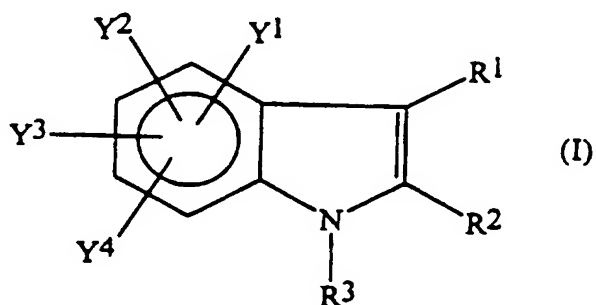
tetrazolyl groups, carboxyl groups, phenyl groups, phenyl substituted with one or more substituents selected from substituents f above, carbamoyl groups, sulfonamide groups, protected sulfonamide groups, carbonylsulfonamide groups, hydroxyl groups, alkoxy groups having 1 to 6 carbon atoms, thiol groups, alkylthio groups having from 1 to 6 carbon atoms, aryl groups, heterocyclic groups, carbonyl groups, thiocarbonyl groups, groups of Formula $\text{CONR}^{30}\text{R}^{31}$ wherein R^{30} and R^{31} each represents an alkyl group having from 1 to 6 carbon atoms or, together with the nitrogen to which they are joined form a cyclic or

heterocyclic group, or a group of Formula $\text{CSNR}^{30}\text{R}^{31}$ where R^{30} and R^{31} are as defined above;

PROVIDED THAT not all of Y^1 , Y^2 , Y^3 , Y^4 and R^3 are hydrogen atoms and, when the dotted lines represent single bonds, then any of Y^1 , Y^2 , Y^3 and Y^4 may also represent a keto group and/or any of Y^1 , Y^2 , Y^3 and Y^4 may also represent two such groups Y^1 , Y^2 , Y^3 and Y^4 ,

and pharmaceutically acceptable salts and esters thereof.

28. A compound of formula (I):



wherein:

Y^1 , Y^2 , Y^3 and Y^4 are the same or different and each represents a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl group, a thiol group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms and substituted with a keto group or at least one substituent α defined below, a haloalkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a carboxyl group, a protected

carboxyl group, a sulfonamide group, a protected sulfonamide group or a group of formula $-(O)_p-B^1-T^1$,

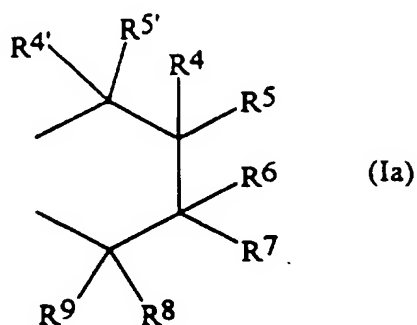
wherein T^1 represents a carboxyl group, a thiocarboxy group, a dithiocarboxy group, a protected carboxyl group, a protected thiocarboxy group, a protected dithiocarboxy group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group, B^1 represents a direct bond or an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α , defined below, and p is 0 or 1;

one of R^1 and R^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group, a substituted aralkyl group, an oxazolyl group, a substituted oxazolyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(A)_p-B^2-T^2$, wherein A represents an oxygen atom or a sulfur atom, T^2 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group, B^2 represents an alkylene group which has from 1 to 6 carbon atoms and which is unsubstituted or has one or more substituents selected from amino groups, protected amino groups, hydroxyl groups, protected hydroxyl groups, oxazolyl groups and substituted oxazolyl groups, and p is as defined above;

and the other of R^1 and R^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group or a substituted aralkyl group;

or

R^1 and R^2 together represent a group of formula (Ia):



[in which R^4 and $R^{4'}$ are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms;

R^5 and $R^{5'}$ are the same or different and each represents a hydrogen atom or a group of formula $-(O)_p-(CH_2)_n-T^3$ in which T^3 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and $n=0, 1$ or 2 , and p is as defined above;

R^6 represents a hydrogen atom or a hydroxyl group;

R^7 represents a hydrogen atom, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^3-T^4$ in which T^4 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and B^3 represents an alkylene group which has from 1 to 4 carbon atoms and which

is unsubstituted or is substituted by at least one of substituents α , and p is as defined above;

R^8 represents a hydrogen atom;

or

when R^9 represents an alkylthio group having from 1 to 6 carbon atoms, R^7 and R^8 together represent a lactone group;

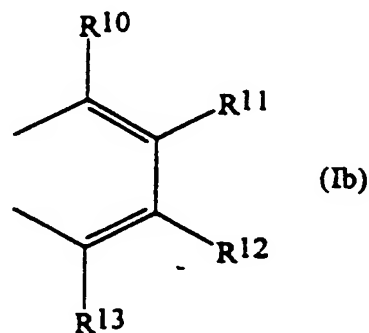
R^9 represents a hydrogen atom or an alkylthio group having from 1 to 6 carbon atoms;

or

R^8 and R^9 together represent an oxo group];

or

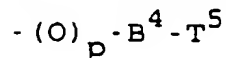
R^1 and R^2 together represent a group of formula (Ib):



[in which R^{10} , R^{11} , R^{12} and R^{13} are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a hydroxyalkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected

- 323 -

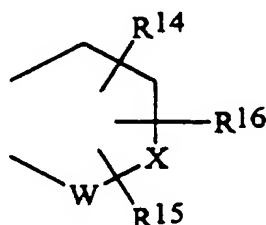
carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula



in which T^5 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group, B^4 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α , and, and p is as defined above];

or

R^1 and R^2 together represent a group of formula (Ic):



(Ic)

[in which R^{14} represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a hydroxy-alkyl group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p \cdot B^4 \cdot T^5$ in which T^5 , B^4 and p are as defined above; R^{15} and R^{16} are the same or different, and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group; Z is a methylene group, a group of formula $>NH$ or a group of formula $>N-$, and W is

a methylene group, a sulfur atom or a group of formula $>S-(O)_q$, where q is 0, 1 or 2, preferably 1 or 2, provided that at least one of W and Z is a methylene group);

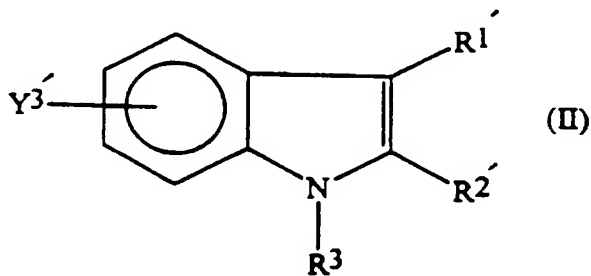
R^3 represents a hydrogen atom or an amino protecting group;

and

said substituents α are hydroxyl groups, aryl groups, aralkyl groups and substituted aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

29. A compound of formula (II):



wherein:

Y^3 represents a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group, a substituted aralkyl group, or, when both $R^{1'}$ and $R^{2'}$ are hydrogen atoms, a group of formula $-B-T$, wherein T

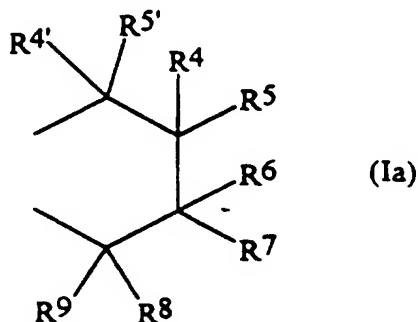
represents a carboxyl group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group and B represents an alkylene group having from 1 to 4 carbon atoms and being optionally substituted by a phenyl or benzyl group, said phenyl or benzyl group being optionally substituted by one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

$R^{1'}$ represents a hydrogen atom or a group of formula -B'-T', wherein T' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and B' represents an alkylene group having from 1 to 4 carbon atoms and being optionally substituted by an amino group;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ia):



[in which R^4 and $R^{4'}$ are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms;

R^5 and $R^{5'}$ are the same or different and each represents a hydrogen atom or a group of formula $-(CH_2)_n-T''$ in which T'' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and $n=0, 1$ or 2 ;

R^6 represents a hydrogen atom or a hydroxyl group;

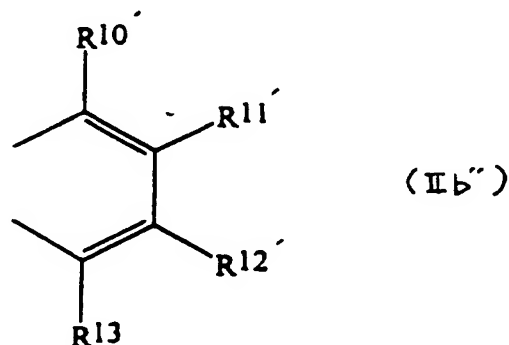
R^7 represents a hydrogen atom or a group of formula $-(CH_2)_m-T'''$ in which T''' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and $m=0, 1$ or 2 ;

R^8 represents a hydrogen atom or, together with R^6 , represents a lactone group;

R^9 represents a hydrogen atom, a keto group or a methylthio group];

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ib''):



[in which $R^{10'}$ represents a hydrogen atom or an

alkyl group having from 1 to 6 carbon atoms;

$R^{11'}$ represents a hydrogen atom or a group of formula $-(CH_2)_n-T''$ in which T'' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and n is as defined above;

$R^{12'}$ represents a hydrogen atom, a hydroxyl group, a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B''-T'''$ in which T''' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group, $p=0$ or 1 and B'' represents an alkylene group having from 1 to 4 carbon atoms and being optionally substituted by a hydroxyl group, a phenyl group or a benzyl group, said phenyl or benzyl group being optionally substituted by one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

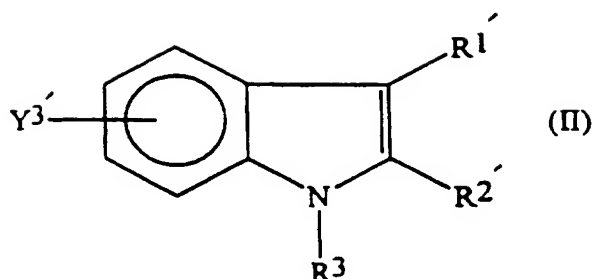
R^{13} represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, or a methylthio group];

and

R^3 represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms substituted with a keto group and/or a phenyl group, said phenyl group being optionally substituted with one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

and pharmaceutically acceptable salts and esters thereof.

30. A compound of formula (II):



wherein:

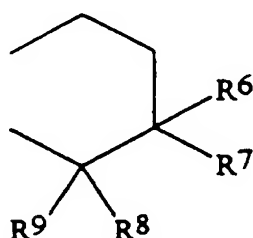
one of $R^{1'}$ and $R^{2'}$ represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group, a substituted aralkyl group, an oxazolyl group, a substituted oxazolyl group which is substituted by at least one of substituents β' , defined below, a group of formula $-(A)_p-B^5-COOH$, where A represents an oxygen atom or a sulfur atom, p is 0 or 1, B^5 represents an alkylene group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from amino groups, protected amino groups, hydroxyl groups, protected hydroxyl groups, oxazolyl groups and substituted oxazolyl groups;

and the other of $R^{1'}$ and $R^{2'}$ represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group or a substituted aralkyl group;

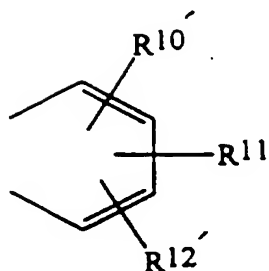
or

$R^{1'}$ and $R^{2'}$ together represent a group of formula

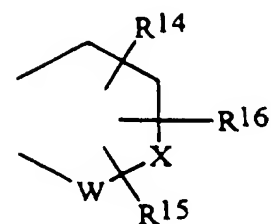
(Id), (Ie) or (Ic):



(Id)



(Ie)



(Ic)

R^{14} and $R^{10'}$ are the same or different and each represents a hydroxy group, a haloalkyl group having from 1 to 6 carbon atoms, a hydroxyalkyl group having from 1 to 6 carbon atoms, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^6-T^6$,

where B^6 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ' , defined below, T^6 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group, and p is as defined above;

R^{15} and $R^{12'}$ are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms, or an aryl group;

Z represents a methylene group, a group of formula $>NH$ or a group of formula $>N-$;

W represents a methylene group, a sulfur atom or a group of formula $>S-(O)_q$, wherein q is as defined above;

provided that at least one of W and Z is a methylene group;

R^{11'} represents a hydrogen atom, a haloalkyl group having from 1 to 6 carbon atoms, or an alkylthio group having from 1 to 6 carbon atoms;

R⁶ represents a hydroxy group;

R⁷ represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula -B⁷-T⁷,

where B⁷ represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ', defined below, and T⁷ represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group;

R⁹ represents a hydrogen atom or an alkylthio group having from 1 to 6 carbon atoms;

or

R⁷ and R⁸ together represent a lactone group, when R⁹ represents an alkylthio group having from 1 to 6 carbon atoms;

or

R⁹ and R⁸ together represent a oxo group;

R³ represents a hydrogen atom or an amino-protecting group;

γ^3 represents a hydrogen atom, a halogen atom, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-B^8-T^8$,

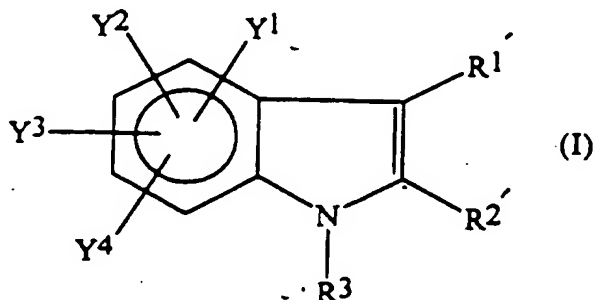
where B^8 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ' , defined below, and T^8 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group;

said substituents β' are selected from alkyl groups having from 1 to 6 carbon atoms, aralkyl groups, substituted aralkyl groups, carboxyl groups, nitro groups, halogen atoms and cyano groups;

said substituents γ' are selected from hydroxy groups, aralkyl groups, and substituted aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

31. A compound of formula (I):



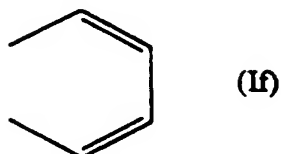
wherein:

$R^{1'}$ represents a hydrogen atom;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula
(If) :



R^3 represents a hydrogen atom, an aralkyl group, an aralkyl group which is substituted by at least one of substituents ϵ , defined below, or an aromatic acyl group;

Y^1 represents a hydrogen atom, a thiol group, an alkyl group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms, a sulfonamide group, a protected sulfonamide group, or a group of formula $-E-COOH$;

Y^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms, a sulfonamide group, a protected sulfonamide group, or a group of formula $-E-COOH$ or $-E-Tet$, where Tet represents a tetrazolyl group;

Y^3 represents a haloalkyl group having from 1 to 6 carbon atoms, a sulfonamide group, a protected

sulfonamide group, a group of formula -E-COOH or -E-Tet, where Tet is as defined above;

Y^4 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms or a halogen atom; and

E represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ' , defined below, or an oxyalkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ' , defined below;

PROVIDED that

(1) when $R^{1'}$ and $R^{2'}$ both represent hydrogen atoms, at least one of Y^1 , Y^2 and Y^3 represents a group of formula -E-COOH and R^3 does not represent a hydrogen atom;

(2) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group and R^3 represents a hydrogen atom, Y^1 , Y^2 and Y^4 do not all represent hydrogen atoms;

(3) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group, Y^2 represents a hydrogen atom, and one of Y^1 and Y^4 represents a carboxy group, R^3 does not represent a hydrogen atom;

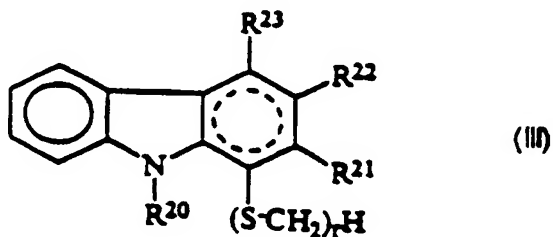
(4) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group, and at least one of Y^1 , Y^2 and Y^4 represents an alkyl group, R^3 does not represent a hydrogen atom;

(5) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group and Y^4 represents a halogen atom, Y^1 and Y^2 do not both represent hydrogen atoms;

said substituents γ' are selected from alkyl groups having from 1 to 6 carbon atoms, aralkyl groups, and aralkyl groups substituted by at least one of substituents ϵ , defined below;

said substituents ϵ are selected from halogen atoms and nitro groups.

32. A compound of formula (III):



wherein:

the dotted circle indicates that the ring in which it is present is fully unsaturated;

R^{20} represents a benzyl group optionally substituted with one or more substituents selected from halogen atoms, amino groups, nitro groups and hydroxy groups;

R^{21} represents a group of formula $-Q-Alk-COOH$ wherein

Q represents an oxygen atom or a direct bond and Alk represents a lower alkylene group, Alk optionally being substituted with a benzyl group optionally further substituted with one or more substituents selected from halogen atoms, amino groups, nitro groups and hydroxy groups;

R^{22} represents a hydrogen atom;

R^{23} represents a hydrogen atom or a lower alkyl group; and

$r=0$ or 1 ;

OR

the dotted circle indicates that the core triple ring structure is a 1,2,3,4-tetrahydrocarbazole;

R^{20} , R^{21} and R^{23} all represent hydrogen atoms and R^{22} represents a lower alkyl group substituted with a carboxyl group;

and $r=1$.

33. The compound of claim 1, in which:

Y^1 , Y^2 and Y^4 each represents a hydrogen atom;

Y^3 represents a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a carboxyl group, a protected carboxyl group or a group of formula $-(O)_p-B^1-T^1$,

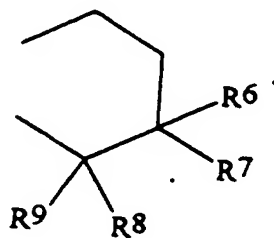
wherein T^1 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group, B^1 represents an alkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α' , defined below, and p is 0 or 1;

$R^{1'}$ represents a hydrogen atom, a carboxyl group, a protected carboxyl group, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group, a substituted aralkyl group or a group of formula $-B^2-COOH$, wherein T^2 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group, B^2 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by an amino group or a protected amino group;

$R^{2'}$ represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group, a substituted aryl group, an aralkyl group or a substituted aralkyl group;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Id):



(Id)

[in which R^6 represents a hydrogen atom or a hydroxyl group;

R^7 represents a hydrogen atom, a carboxyl group, a protected carboxyl group, or a group of formula $-B^3-T^4$ in which T^4 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group and B^3 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ' ;

R^9 represents a hydrogen atom or an alkylthio group having from 1 to 6 carbon atoms;

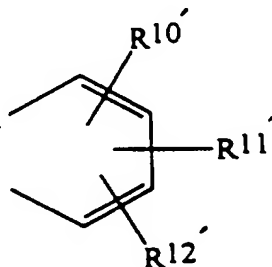
when R^9 represents an alkylthio group, R^7 and R^8 together represent a lactone group;

or

R^8 and R^9 together represent an oxo group];

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ie):



(Ie)

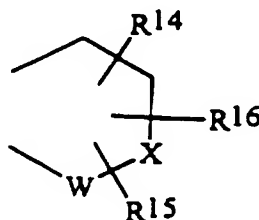
[in which $R^{10'}$ represents a hydroxyalkyl group

having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group, or a group of formula $-(O)_p-B^4-T^5$

in which T^5 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group, B^4 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ' , and, and p is as defined above];

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ic):



(Ic)

[in which R^{14} represents a hydroxyalkyl group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group or a group of formula $-(O)_p-B^4-T^5$ in which T^5 , B^4 and p are as defined above; R^{15} and R^{16} are the same or different, and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group; and Z is a methylene group, a group of formula $>NH$ or a group of formula $>N-$];

R^3 represents a hydrogen atom or an amino protecting

group;

and

said substituents α' are hydroxyl groups, aryl groups and aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

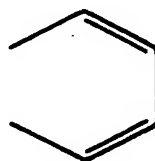
34. The compound of claim 1, in which:

$R^{1'}$ represents a hydrogen atom;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (If):



(If)

R^3 represents a hydrogen atom, an aralkyl group, an aralkyl group which is substituted by at least one of substituents ϵ , defined below, or an aromatic acyl group;

Y^1 represents a hydrogen atom, an alkyl group having from 1 to 3 carbon atoms or a group of formula $-E'-COOH$;

Y^2 represents a hydrogen atom, an alkyl group having

from 1 to 3 carbon atoms, an alkylthio group having from 1 to 3 carbon atoms or a group of formula $-E'-COOH$ or $-E'-Tet$, where Tet represents a tetrazolyl group;

Y^3 represents a group of formula $-E'-COOH$ or a group $-E'-Tet$, where Tet is as defined above;

Y^4 represents a hydrogen atom, an alkyl group having from 1 to 3 carbon atoms or a halogen atom; and

E' represents a direct bond, an alkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ' , defined below, or an oxyalkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ' , defined below;

and pharmaceutically acceptable salts and esters thereof.

35. The compound of claim 34, wherein $R^{1'}$ and $R^{2'}$ together represent a group of formula (If).

36. The compound of claim 34, wherein R^3 represents an aralkyl group, an aralkyl group having one or more of substituents β' or an aromatic acyl group.

37. The compound of claim 34, wherein R^3 represents an aralkyl group or an aralkyl group having one or more of substituents β' .

38. The compound of claim 34, wherein R^3 represents a benzyl group or a benzyl group having one or more of substituents β' .

39. The compound of claim 34, wherein Y^1 represents a hydrogen atom, a group of formula $-E'-COOH$, or a group

of formula -E'-Tet, wherein Tet is a tetrazolyl group.

40. The compound of claim 34, wherein Y^1 represents a hydrogen atom.

41. The compound of claim 34, wherein Y^2 represents a hydrogen atom, an alkylthio group having from 1 to 6 carbon atoms, a group of formula -E'-COOH, or a group of formula -E'-Tet, wherein Tet is a tetrazolyl group.

42. The compound of claim 34, wherein Y^2 represents an alkylthio group having from 1 to 3 carbon atoms.

43. The compound of claim 34, wherein Y^2 represents an alkylthio group having from 1 to 6 carbon atoms.

44. The compound of claim 34, wherein Y^2 represents an alkylthio group having from 1 to 3 carbon atoms.

45. The compound of claim 34, wherein Y^4 represents a halogen atom or an alkyl group having from 1 to 6 carbon atoms.

46. The compound of claim 34, wherein Y^4 represents an alkyl group having from 1 to 3 carbon atoms.

47. The compound of claim 34, wherein E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α' , an oxyalkylene group having from 1 to 3 carbon atoms or a substituted oxyalkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α' .

48. The compound of claim 34, wherein E' represents a direct bond, an alkylene group having from 1 to 3 carbon

atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α' , or an oxyalkylene group having from 1 to 3 carbon atoms.

49. The compound of claim 34, wherein E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, an alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one substituent selected from the group consisting of aralkyl groups and aralkyl groups substituted by at least one of substituents β' , an oxyalkylene group having from 1 to 3 carbon atoms or a substituted oxyalkylene group which has from 1 to 3 carbon atoms and is substituted by at least one substituent selected from the group consisting of aralkyl groups and aralkyl groups substituted by at least one of substituents β' .

50. The compound of claim 34, wherein E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one substituent selected from the group consisting of aralkyl groups and aralkyl groups substituted by at least one of substituents β' , or an oxyalkylene group having from 1 to 3 carbon atoms.

51. The compound of claim 1 for use in the treatment of dementia.

52. The compound of claim 1 for use in the treatment of Alzheimer's disease and delirium.

53. The compound of claim 1 for use as sedatives for the central nervous system.

54. The compound of claim 1 for use in the manufacture

of a medicament for the treatment of Alzheimer's disease.

55. A method of regulating m1 receptor response in vivo in a mammalian subject, comprising the step of administering to said subject an effective amount of a selective allosteric effector to regulate said receptor.

56. The method of claim 54 wherein the allosteric effector exhibits positive cooperativity with acetylcholine at said receptor.

57. The method of claim 54 wherein said selective allosteric effector is the compound of claim 1.

58. The method of claim 54 wherein said selective allosteric effector is the compound of claim 2.

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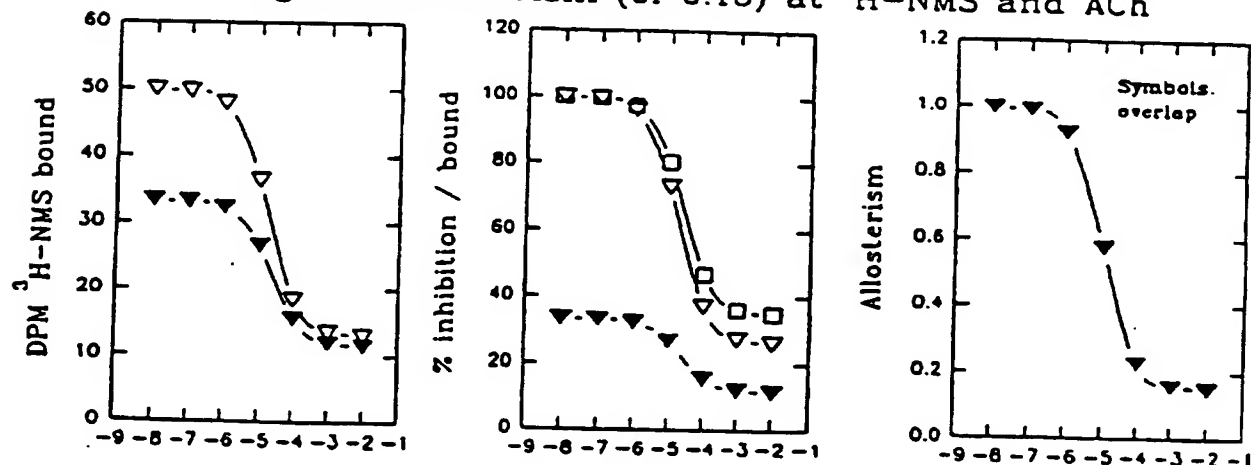
FIG. 1a

Theoretical curves of effect of allosteric agent
on binding of ^3H -NMS alone and with ACh

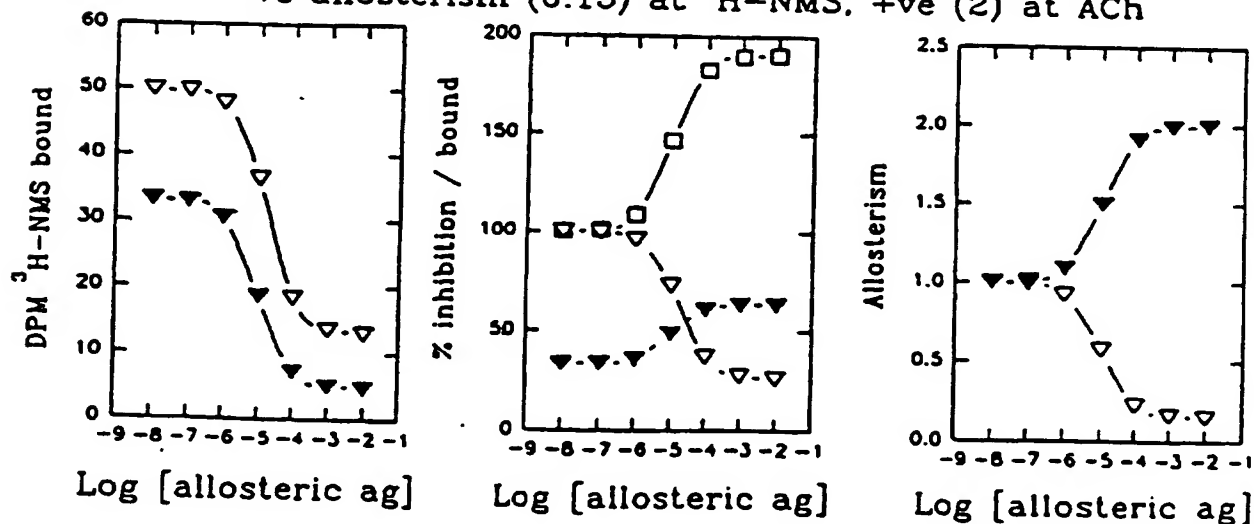
$$K_{^3\text{H-NMS}} = 10^{10}, K_{\text{ACh}} = 10^5, \text{ both at the } K_d \text{ concentration}$$

$$K_{\text{allosteric ag}} = 10^5$$

Negative allosterism (of 0.15) at ^3H -NMS and ACh



-ve allosterism (0.15) at ^3H -NMS, +ve (2) at ACh



▽ ^3H -NMS alone
▼ + ACh

▽ total % no allo
▼ ACh % inhib of total
□ ACh % control inhib

▽ ^3H -NMS alone
▼ + ACh

2/3

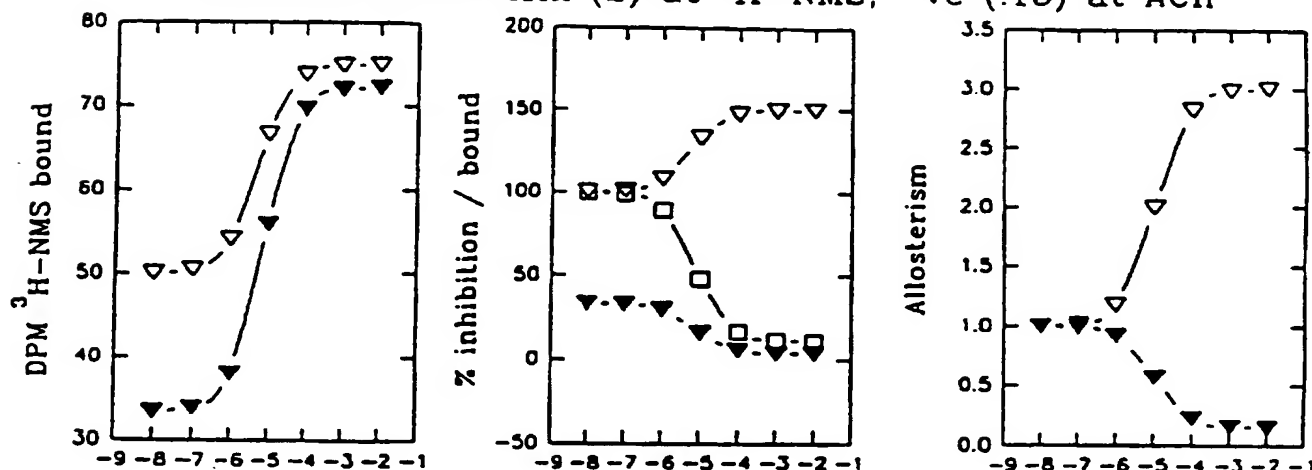
FIG. 1b

Theoretical curves of effect of allosteric agent
on binding of ^3H -NMS alone and with ACh

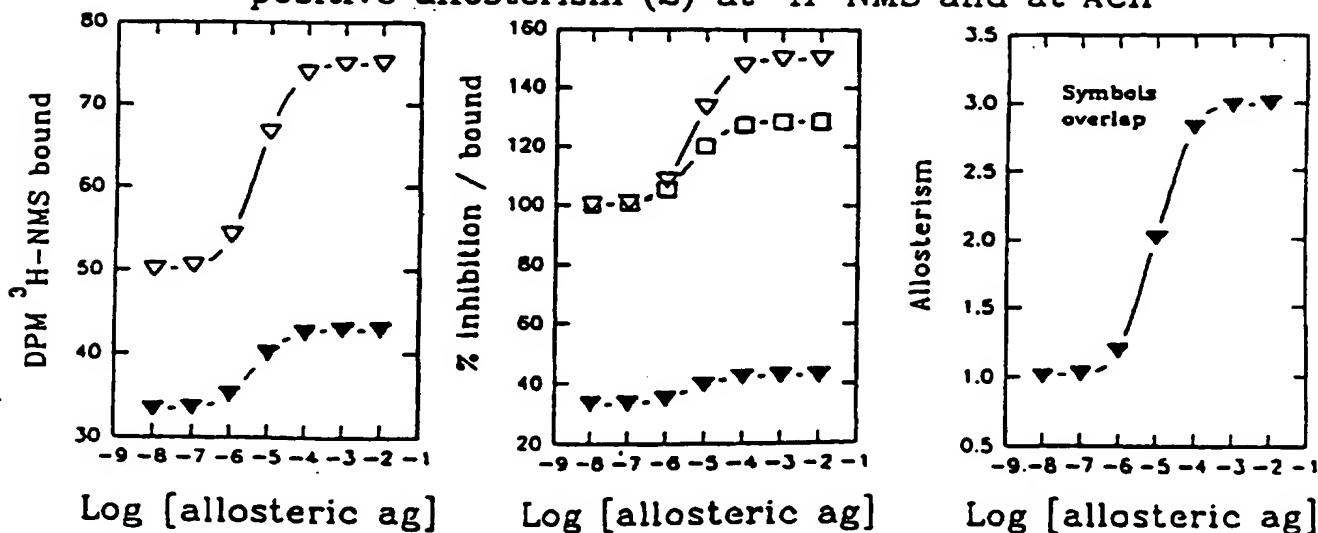
$K_{^3\text{H-NMS}} = 10^{10}$, $K_{\text{ACh}} = 10^5$, both at the K_d concentration

$K_{\text{allosteric ag}} = 10^5$

Positive allosterism (2) at ^3H -NMS, -ve (.15) at ACh



positive allosterism (2) at ^3H -NMS and at ACh



▽ ^3H -NMS alone
▼ + ACh

▽ total % no allo
▼ ACh % inhib of total
□ ACh % control inhib

▽ ^3H -NMS alone
▼ + ACh

3/3

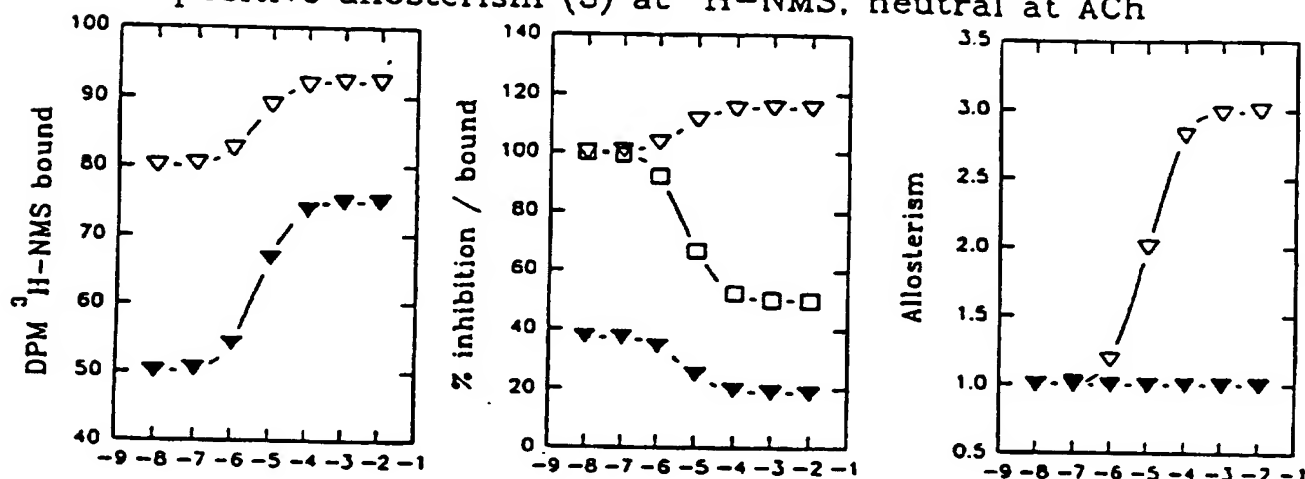
FIG. 1c

Theoretical curves of effect of allosteric agent
on binding of ^3H -NMS alone and with ACh

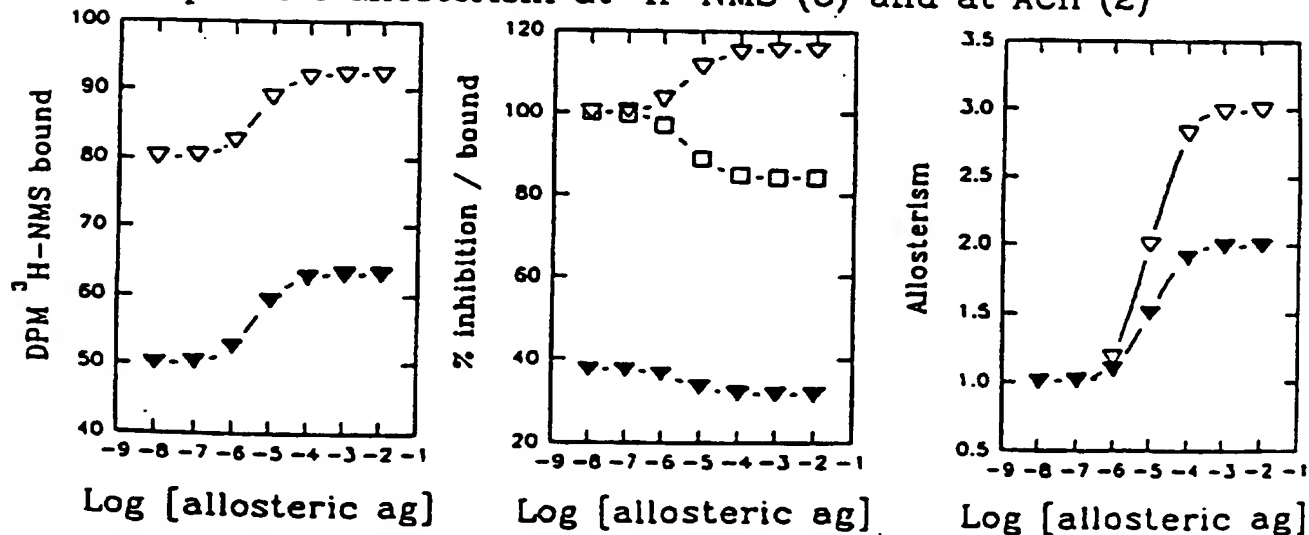
$$K_{^3\text{H-NMS}} = 10^{10}, K_{\text{ACh}} = 10^5, [^3\text{H-NMS}] = 0.4\text{nM}, [\text{ACh}] = 30\mu\text{M}$$

$$K_{\text{allosteric ag}} = 10^5$$

positive allosterism (3) at ^3H -NMS, neutral at ACh



positive allosterism at ^3H -NMS (3) and at ACh (2)



▽ ^3H -NMS alone
▼ + ACh

▽ total % no allo
▼ ACh % inhib of total
□ ACh % control inhib

▽ ^3H -NMS alone
▼ + ACh

INTERNATIONAL SEARCH REPORT

Intern² application No
PCT/JP 95/01494

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D209/88 C07D209/86 C07D209/42 C07D209/08 C07D495/04 C07D471/04 C07D403/06 C07D403/04 C07D401/06 A61K31/41 A61K31/40		
According to International Patent Classification (IPC) or to both national classification and IPC.		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 200 419 (WARNER-LAMBERT COMPANY) 6 April 1993 see column 3, line 60 - column 4, line 61 ---	1-6, 27-30, 51-58
X,P	PATENT ABSTRACTS OF JAPAN vol. 940, no. 10 (0-00000) & JP,A,06 298 732 (TAISHO PHARMACEUTICAL CO., LTD.) 25 October 1994 see abstract --- -/-	1-58
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 14 September 1995		Date of mailing of the international search report 27. 09. 95
Name and mailing address of the ISA European Patent Office, P.O. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl. Fax (+ 31-70) 340-3016		Authorized officer Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internatⁿ application No
PCT/JP 95/01494

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 99, no. 13, 26 September 1983, Columbus, Ohio, US; abstract no. 99889a, M. SKUP ET AL. 'In vitro studies on the effect of beta-carbolines on the activities of acetylcholinesterase and choline acetyltransferase and on the muscarinic binding of the rat brain.' page 139 ;	27-30
Y	see abstract & JOURNAL OF NEUROCHEMISTRY, vol.41, no.1, 1983, NEW YORK pages 62 - 68	1,27-30, 51-58
Y,P	--- CHEMICAL ABSTRACTS, vol. 121, no. 9, 29 August 1994, Columbus, Ohio, US; abstract no. 99051u, M. DEKHANE ET AL. 'N-2 methylated quarternary derivatives of beta-carboline-3-carboxylates inhibit acetylcholinesterase in vitro.' page 21 ; see abstract	1,27-30, 51-58
Y	& BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol.3, no.12, 1993, OXFORD pages 2831 - 2836	1,27-30, 51-58
A	--- EP,A,0 548 664 (F. HOFFMANN-LA ROCHE AG) 30 June 1993 see the whole document -----	1-58

INTERNATIONAL SEARCH REPORT

I International application No.

PCT/JP 95/01494

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 55-58 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The subject matter of the present application is so broad that a complete search is not possible on economic grounds, e.g. independent claims 29 and 30 cover very simple and well-known compounds such as indole. Therefore the search has been based on examples and the claims as indicated (PCT Search Guidelines III, 3.6). Claims searched incompletely: 1-33, 51-58
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Intern: application No
PCT/JP 95/01494

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5200419	06-04-93	NONE	
EP-A-0548664	30-06-93	AT-T- 123277	15-06-95
		AU-B- 661076	13-07-95
		AU-A- 3018692	24-06-93
		CA-A- 2084442	21-06-93
		CN-A- 1088576	29-06-94
		DE-D- 59202406	06-07-95
		HU-A- 68178	29-05-95
		JP-A- 6128228	10-05-94
		NZ-A- 245463	26-05-95
		US-A- 5318966	07-06-94
		US-A- 5318967	07-06-94